THE 1983 REPORT OF
THE NATIONAL ADVISORY EYE COUNCIL

Volume One

VISION research

A NATIONAL PLAN

1983-1987

U.S. DEPARTMENT OF HEALTH
AND HUMAN SERVICES
Public Health Service
National Institutes of Health

NATIONAL ADVISORY EYE COUNCIL

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FOREWORD

THE PUBLICATION OF Vision Research—A National Plan: 1983–1987 by the National Advisory Eye Council is a major milestone in the history of the National Eye Institute. Never before have so many scientists representing such a broad and diverse range of disciplines, interests, and backgrounds participated in so comprehensive an effort to identify research needs and opportunities and establish priorities for the support of vision research.

In preparing this third in a series of five-year National Plans the Council attempted to assess the entire field of vision research in greater depth than ever before, even including areas not currently supported by the National Eye Institute. To facilitate the evaluation and planning process and to increase the comprehensibility of the Plan, the Council took pains to adopt a uniform approach to examining each program and subprogram. This has not been an easy task, given the number, variety, and complexity of the scientific areas addressed and the large number of individuals involved in the planning process and their geographic dispersion. That the Plan is so complete and stresses research relevant to the interests of the clinician, while continuing to place strong emphasis on critical areas of basic research, is to the great credit of Dr. Thomas D. Duane, who chaired the Council's Program Planning Subcommittee which oversaw the entire planning process.

The value of these National Plans to the NEI staff has been inestimable. They have made it easier to develop and maintain a consistent policy that guides the day-to-day management of the Institute's affairs and to develop and implement a long-range strategy for program growth and development. They have provided the Council with a rational basis for determining the program relevance of the grant applications they review. And, they have provided this support while allowing great flexibility to capitalize on unforeseen opportunities as they have occurred.

It cannot be stressed too strongly that, despite its comprehensiveness and detail, this Plan will serve as only a guide to the Council and NEI staff over the next five years. The key determinant of what research the NEI will support will continue to be the proposals we receive for research grants whose quality is judged by the peers of the scientists who develop them. The National Plan is intended to augment, not supplant, the time-honored NIH peer review system. The way in which the Plan interacts with the NIH grant review process is described in detail in this Volume, and this explanation warrants the attention of anyone interested in the development of the National Eye Institute's program.

Over the next five years, the NEI will carefully monitor how closely the Institute's actual program development matches the recommendations of the Plan. From this tracking we hope to identify areas in which additional measures may be required to stimulate needed research and possibly to find areas in which the Plan's recommendations should be modified. Such monitoring should also help us improve our evolving planning process. In this regard, we also will be pleased to receive any comments or suggestions from readers that will help in further refining this effort.

CARL KUPFER, M.D.
Director
National Eye Institute

PREFACE

THE MISSION OF the National Eye Institute as defined in its authorizing legislation is straightforward: find new ways to prevent, diagnose, and treat diseases of the visual system, thus preventing and possibly eliminating blindness. Although this mandate is explicit, recent developments in scientific concepts and technology are so prolific that no one individual, no matter how well informed, can understand and appreciate them all, let alone know what research should be emphasized so that society will benefit maximally. Optimal distribution of the research dollar, whether from the Federal Government, private industry, or philanthropy, is extremely difficult, but especially in times of fiscal stringency it is a goal toward which we must strive.

In 1973 the National Advisory Eye Council, members of which are appointed for a term of four years by the Secretary of Health and Human Services, first decided to assay the present state of vision research by asking a few key leaders in the various scientific disciplines thereof to survey their fields and areas of interest so that they could document what was known and what needed more exploration and elucidation, that is, determine what were the most important research needs and opportunities. Under the imaginative leadership of Bradley R. Straatsma, M.D., and with the unstinting assistance of the energetic and informed staff of the National Eye Institute, a two-volume document was published in 1976: *Vision Research Program Planning.*

This pioneering document proved to be so successful in defining basic principles and guidelines for vision research planning which were acceptable to the Council, the NEI, and research community alike that the National Advisory Eye Council decided next to produce a comprehensive and detailed national vision research Plan.

In 1977, under the able chairmanship of A. Edward Maumenee, M.D., a thorough documentation of the current state of eye research and the most likely course for profitable research in the subsequent five years was completed. In this effort, the Council employed Panels of experts from all fields of vision research and ophthalmology and the staff of the National Eye Institute. This remarkable three-volume set, *Vision Research—A National Plan: 1978–1982*, has influenced the Congress, the National Institutes of Health, the Department of Health and Human Services, investigators in the field, and the public at large.

Based on the experience of the previous Council reports, the present document attempts to define and assess the base upon which knowledge and investigation in the visual system has been built. Members of the Council, aided by 350 consultants, have attempted to predict where vision research is headed and what looks most promising in the near future. We believe we should not only prognosticate and outline the opportunities which lay ahead, but we should weigh them and evaluate their likelihood of succeeding. Because we believe that it is our responsibility to state what we think represents the best chance of producing solid scientific results in the near future, we, the members of the National Advisory Eye Council in collaboration with the Panels, have recommended to the NEI program priorities which we believe will help us and our successors guide the Institute in achieving its goals and objectives in the most timely manner practicable.

A few words should be said about the scientific base of vision research and the concept of defining what we believe will be promising areas for NEI program development. One can look upon scientific endeavor in the field of vision research as a structure with the proportions of a pyramid. Although physicians and scientists have been building the base of technological skills and knowledge for several thousand years, only in the last 15 years, as judged by the writers and editors of journals and

textbooks, has the greatest accelerated expansion of research effort and knowledge occurred.

We are ready to continue this extension upward, and we think we can best encourage this progress by setting priorities for research funding. But there is an aspect of this activity that seems to cause confusion and consternation in the minds of some researchers. When the Council recommends priorities for the next phase of growth in the National Eye Institute's support of eye research, we do not mean that only new areas of research will be supported. We fully appreciate that the pyramidal research base is incomplete and imperfect and that it needs shoring and modification. We have no intention of abandoning sound studies of the fundamentals upon which eye research is based.

In other words, we do not want to encourage scientists to strive exclusively for breakthroughs according to a rigid formula established by the Council and its consultants. On the other hand, we would be remiss in financing the reinvention of the wheel. In short, a sound hypothesis backed by a well-written application for support of a research project to test it will always have priority for funding.

There is also another concern—that of the balance between support for basic science and support for clinical science. The Council believes that to advance vision science and to accomplish the mission of the National Eye Institute, we need to give support to both basic and clinical scientists who seem to have the best chances of producing answers to the most pressing problems in the field. With *Vision Research—A National Plan: 1983-1987*, we hope to attain several goals:

First, to provide a summary of the state of the art in vision research, divided into the categories of the five principal NEI extramural research programs: Retinal and Choroidal Diseases; Corneal Diseases; Cataract; Glaucoma; and Strabismus, Amblyopia, and Visual Processing; and for the special area of Visual Impairment and Its Rehabilitation;

Second, to present our judgments regarding the timeliness and value of proposed research investigations;

Third, to estimate how much the research we recommend will cost;

Fourth, to explain how we expect this National Plan to influence the research community and how this will be tracked in future years;

Fifth, to demonstrate how vision research is related to broad scientific topics of national concern; and

Sixth, to put these decisions and how they were determined into focus for the investigator, practitioner, Congressman, Administration official, research administrator, interested patient, and taxpaying citizen.

In summary, the members of the National Advisory Eye Council, with the aid of numerous experts from the scientific community, have in *Vision Research—A National Plan: 1983-1987* documented the extent of the problem of visual disorders and blindness and assessed virtually all recent research aimed at its solution. Based on this appraisal we have outlined what we believe to be today's most urgent research needs and examined existing and potential opportunities for meeting them. Furthermore, because we believe we should not merely list such opportunities, but evaluate their likelihood of succeeding, we have set research priorities and estimated their cost.

We will implement these priorities by always supporting the best basic and clinical research proposals we receive and, when necessary, by taking special measures to help ensure that our goals are met. To accomplish this we seek the support of the vision research community, other scientists, and all those who share our interest in eradicating blindness and visual disability.

THOMAS D. DUANE, M.D., PH.D.
Chairman
Program Planning Subcommittee
National Advisory Eye Council

OVERVIEW

THIS IS THE 1983 Report of the National Advisory Eye Council, which is *Volume One,* of the multivolume report entitled, *Vision Research—A National Plan: 1983–1987.*

The complete National Plan presents a comprehensive and detailed assessment of the current NEI program as well as specific recommendations for program development over the next five years. These include program priorities and projections of resource requirements for each major area of vision research that the NEI supports. Readers desiring additional information should consult the following volumes:

Executive Summary (Overview of the entire Plan).

Volume One—The 1983 Report of the National Advisory Eye Council (Background, Summary Panel Reports and Resource Requirements, Implementation Strategy, Cross-Cutting Research Areas and Issues, Planning Participants, Planning Strategy and Process).

Volume Two—Reports of the Program Panels

Part One—*Report of the Retinal and Choroidal Diseases Panel*

Part Two—*Report of the Corneal Diseases Panel*

Part Three—*Report of the Cataract Panel*

Part Four—*Report of the Glaucoma Panel*

Part Five—*Report of the Strabismus, Amblyopia, and Visual Processing Panel*

Part Six—*Report of the Panel on Visual Impairment and Its Rehabilitation.*

Volume Three—Support for Vision Research (Data on vision research projects supported by the NEI in FY 1981 and by other government and private organizations in FY 1980).

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INTRODUCTION

BACKGROUND FOR PROGRAM PLANNING

EYE DISEASES AND blindness cause suffering, disability, and loss of productivity for millions of people throughout the world. In the United States alone, over 10 million people suffer from visual impairment that cannot be corrected by eyeglasses or contact lenses. Of these people, 1.5 million are so severely impaired that they cannot read ordinary newsprint. This includes approximately half a million who are legally blind.[1] The leading causes of blindness and visual disability are aging-related maculopathy,[2] cataract, glaucoma, diabetic retinopathy, and optic nerve atrophy.

Although eye disorders can occur at all ages, they are most common among older people. Eye disorders are also among the most frequent birth defects, and developmental eye disorders can have a devastating impact on the child during the critical years of growth and maturity, affecting learning as well as physical and psychological development. Even for a child who has adapted fairly well to low vision or blindness, such a problem provides a formidable barrier to seeking an education and to becoming an independent, self-supporting member of the community.

Serious eye problems can interfere with education and leisure activities, destroy careers, and disrupt family life. Eye and vision disorders rob many elderly people of the rewards of their retirement years, preventing those who are not otherwise handicapped from reading or watching television, moving about unaided, or seeing the faces of friends and loved ones.

Added to the physical and emotional pain and hardship these disorders cause is their staggering economic burden. Recent estimates indicate that eye disorders and blindness cost our nation more than $14 billion annually.

Convinced that visual disorders constituted a major public health problem that could only be solved by placing greater emphasis on vision research, the United States Congress on August 16, 1968, passed Public Law 90–489, authorizing the establishment of a National Eye Institute as part of the Federal Government's National Institutes of Health.

NEI Mission and Growth

The mission of the new Institute, as specified in the law, is to "conduct and support . . . research for new treatment and cures and training relating to blinding eye diseases and visual disorders, including research and training in the special health problems and requirements of the blind and in the basic and clinical sciences relating to the mechanisms of the visual function and preservation of sight."

From an initial appropriation in FY 1970 of $24 million, which included support for approximately 350 individual project grants, the NEI's budget has grown to $118 million in FY 1981, which included support for nearly 900 such investigator-initiated grants. Today, the NEI funds approximately 80 percent of all vision research supported by the Federal Government and national private philanthropic agencies.

This rapid nationwide expansion of support for vision research has been spurred by a number of factors: the submission by qualified scientists of large numbers of high quality proposals for research grants, the high productivity of the vision research community as demonstrated by the numerous advances continually being made in understanding the eye and visual system and improving the ability to prevent, diagnose, and treat various eye disorders; the NEI's insistence on making the individual, investigator-initiated research project grant its mainstay support mechanism; and the strong support of the Congress for the NEI's program.

Yet, none of these factors guaranteed NEI's success. Much depended on how strong a case was made to higher levels within the Executive Branch and the Congress for adequate support of vision research. This was particularly important because the NEI was established at the close of a long period of rapid growth in the Federal support of biomedical research. It was also a time of increasing uncertainty about the stability and continuity of Federal support for biomedical research. This milieu provided an early impetus for NEI to define its program in detail, assess its accomplishments, document research needs and opportunities, and establish priorities for program development.

Vision Research Program Planning

The legislation establishing the NEI authorizes the Secretary of Health and Human Services "to plan for research and training, especially against the main causes of blindness and visual function."

In response to this mandate and to the need to ensure stability, continuity, and accountability in Federal support for vision research, the NEI Director in 1973 asked the Institute's senior advisory body, the National Advisory Eye Council (NAEC), to establish a Program Planning Subcommittee to conduct an extensive analysis of the NEI's program and, with the aid of representatives of the vision research community, formulate recommendations for its development. Since that time, program planning has become an essential and fundamental element in the management of the NEI program. In the short run, planning helps NEI managers provide some measure of continuity and stability of vision research support in response to uncertainties and fluctuations in the annual Federal budget. Over the long run, it provides a systematic means of forecasting the appropriate level of Federal support for vision research. By helping to organize resources and focus attention on the most pressing current research needs and greatest opportunities, research planning can encourage and facilitate advancement in the visual sciences. Finally, through program planning, the NEI fulfills its responsibility to be accountable to the Administration, Congress, and the American people.

The rationale and principles of NEI program planning have been described in the first two reports published by the National Eye Institute and the National Advisory Eye Council.[3,4] These reports have proved valuable to the National Eye Institute staff in formulating policy and in the day-to-day management of NEI programs. They have also been an important resource for responding in a timely and thorough manner to requests for management and program information from those at higher governmental levels and from the public.

The NAEC/NEI program planning system incorporates planning strategies that have been employed successfully elsewhere in government and business, but it has evolved in large part in response to the particular characteristics of the NEI as a biomedical research organization and to the unique aspects of the vision research program that NEI supports. The approach has been detailed, but pragmatic and flexible; specific, but not dogmatic. And, the planning process has been broadly inclusive; attempts have been made to involve as large and diverse a group of scientific interests and expertise as possible, both from within and outside the vision research community. (See "Appendix")

The National Plans

The first Council report, *Vision Research Program Planning*, a two-volume publication covering the years 1976–1979, issued in April 1975, established the principles and guidelines for National Eye Institute program planning. It articulated a philosophy of planning which attempts to balance the need to allow scientific creativity to flourish freely with the need to identify specific program priorities and policies for the NEI to follow in ensuing years. The report also provided the first systematic examination of the Institute's total program, including data that could serve as a basis for further evaluation and planning.

In 1978, a second report, *Vision Research—A National Plan: 1978–1982*, was published that updated and greatly expanded upon the previous report. This three-volume document, prepared with the help and advice of more than 150 consultants from the vision research community, outlined for the first time specific NEI program goals and objectives, described accomplishments and research needs and opportunities in detail, and identified priorities in each of the five disease-oriented programs which the NEI extramural (grants and contracts) program then comprised: Retinal and Choroidal Diseases, Corneal Diseases, Cataract, Glaucoma, and Sensory and Motor Disorders of Vision. A special report on Vision Research Training was also included. Another feature was a five-year Council budget based upon a detailed grant-by-grant analysis of the existing program and a quantitative estimate of future resource requirements based on current research needs and opportunities.

The purpose of this budget, which was developed by the Council independent of the NEI's official budgetary process, was to provide a rational estimate of the resources required to carry out all of the Plan's recommendations. In developing this estimate the Council was fully aware that many factors—political, social, economic—other than research needs influence the development of the

NEI's actual budget. However, the Council believed that any credible research plan must include an assessment of resource requirements to guide those in Government who make the final decisions about the level of support provided for vision research.

Principles

Four general principles, first outlined in the Council's 1975 report, continue to guide the NEI/NAEC planning process:

- Planning procedures must not disrupt the NEI's successful ongoing research program.
- The NIH investigator-initiated research project grant (R01) must be relied upon as the primary mechanism of research support.
- The NIH peer review process must continue to be used for the initial assessment of the scientific merit of proposals for individual research projects.
- The planning process must be prospective and continuous and its outcome should be communicated promptly to the scientific community and the general public.

Guidelines

In addition to these general principles, the Council continues to endorse the following guidelines developed during its initial planning process.

- Continue to fund first all proposals for research projects that are judged to be of the highest scientific quality by NIH Study Sections and other initial NIH peer review groups.
- Emphasize research which is most relevant to the prevention, diagnosis, and treatment of blinding and visually disabling disorders.
- Stress basic biological and applied clinical research on problems related to the most common causes of blindness and visual disability.
- When research involves laboratory animals, favor the utilization of species for which both scientific opportunity and technical feasibility permit the greatest amount of generalization to the human condition.

Current Need

Today, the need for comprehensive vision research program planning at the national level continues. The enormous magnitude of the problem of blindness and visual disability in the United States—and indeed throughout the world—and the fact that there are many more opportunities for productive research than there are funds and trained manpower to carry them out require an ongoing system for the rational allocation of available research resources to areas of the greatest need, importance, and promise.

The NEI/NAEC approach to program planning is based upon careful and detailed assessments by experts of the extent of the problem of visual disorders and blindness, past accomplishments, current research needs and opportunities, and the resources required for further advance. Based on this evaluation, the Council identifies areas of particular importance and promise as Program Development Priorities. Although the need to set priorities is crucial, the NEI program planning process has been kept flexible to allow the staff and Council to accommodate unexpected discoveries that create new areas of opportunity as well as unforeseeable problems that may stymie currently promising areas of inquiry.

The 1983–1987 National Plan

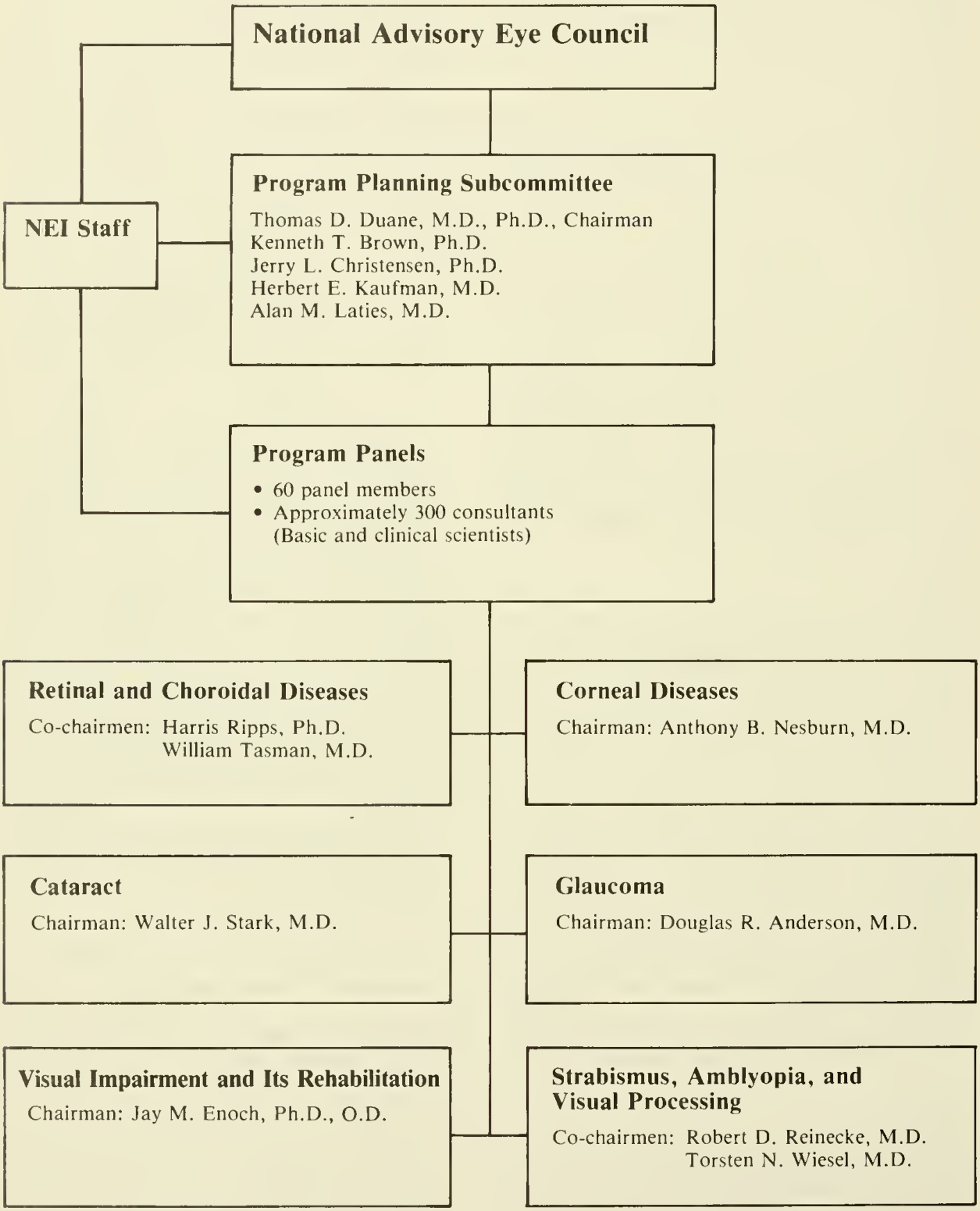
This third National Plan for vision research consists of an Executive Summary; this volume, which is the Council's own report; Volume Two, consisting of six separate and detailed reports of consultant Panels concerning each of the five NEI programs—Retinal and Choroidal Diseases; Corneal Diseases; Cataract; Glaucoma; and Strabismus, Amblyopia, and Visual Processing—and to the cross-program area of Visual Impairment and Its Rehabilitation; and Volume Three, which contains detailed baseline vision research project data used by the Council and its consultants in determining the most important priorities for NEI support of vision research over the next five years. Each Panel report of Volume Two presents a detailed analysis of the status of research in the NEI program it covers and reflects a consensus of Panel members concerning the needs and requirements for continued research progress. The Council's planning organization is shown in Figure 1.

Features of the 1983–1987 National Plan

Each time the Council has developed a new National Plan, an attempt has been made to refine and improve the NEI program planning system. Thus, the strategies and methods used in vision research program planning have evolved over the years. The 1983–1987 Plan is characterized by the following:

- Review and assessment of the entire National Eye Institute program, as well as vision research supported by other organizations, by more than 350 scientists representing all major areas of vision research.

FIGURE 1. Planning Structure



- Revised NEI program structure to improve categorization of current research support and provide a framework for assessing future needs and opportunities in vision research.
- For each NEI program the Plan:
  - Describes the diseases and disorders, including their public health impact, and the research disciplines that the program addresses.
  - Defines program goals and objectives.
  - Surveys current support by the NEI and other organizations.
  - Reviews recent program and research accomplishments.
  - Describes current research needs, opportunities, and approaches.
  - Makes specific recommendations concerning program development.
- Discussion of how the vision research projects the NEI supports relate to the following cross-cutting health science areas and issues, several of which are the subject of considerable national interest for scientific, economic, social, or political reasons:
  - Prevention
  - Diabetes
  - Nutrition
  - Aging
  - Toxicology
  - Genetics
  - Immunology
  - Epidemiology
  - Neurobiology
  - Molecular Biology
  - Noninvasive Research and Diagnostic Techniques
  - Refractive Errors
  - Use of Animals in Vision Research
- For the first time, the Council's recommendations have been grouped according to two categories which together encompass all the research supported by the NEI:
  - *Program Base*—Areas of ongoing research where the current level of activity is considered adequate, or areas of ongoing research in which there may be great need for additional activity, but where, in the Panel's judgment, little or no opportunity (new methods or insights) exists at present to justify a significant expansion of effort.
  - *Program Development Priorities*—Areas of ongoing research in which new knowledge and techniques offer particular opportunities for scientific progress, or promising new areas of research in which there is little or no support at present but where there is both great need and high potential for success. Such areas are judged to warrant significantly increased support over the next five years, provided that high quality applications for research grants in these are forthcoming.

With this third National Plan, the Council hopes, as before, to encourage additional research in important areas where activity is low, to stimulate new research in important areas where currently no work is being performed, and to maintain important areas where there is already a considerable amount of research support.

Priorities

It is important to understand that the term "priority" as applied to the NEI program has several meanings. As used in this document, a priority is a research need judged to be of particular importance in terms of fulfilling a program goal; it is not a reference to the scientific merit "priority scores" assigned by NIH study sections to the grant applications they review. It is in areas designated as Program Development Priorities that most recommendations for additional funds and projects are made. The relationship of the scientific merit priority scores to the Program Development Priorities of the NEI as outlined in this National Plan is discussed in the next section. At this point, however, it may be useful to distinguish clearly among these and other kinds of priorities as they pertain to the NEI.

- *Funding priorities* for the award of NEI grants are based primarily on the scientific merit priority scores assigned by NIH study sections and other NIH and NEI initial peer review groups; those grants receiving the best (numerically lowest) scores are given primary consideration for funding.
- The *highest priority NEI support mechanism* is the individual, investigator-initiated research project grant (R01).
- The NEI's *highest priority research goal* is the prevention of major blinding and disabling eye conditions.

- Within each of the NEI's five major programs *Program Development Priorities* are outlined in this National Plan.

Implementation of the National Plan

As stated above, the individual, investigator-initiated NIH research project grant continues to be the NEI's highest priority funding mechanism. For this reason, the successful implementation of this National Plan will depend largely upon scientists submitting high quality grant applications for research in areas which the Council and the planning Panels have recommended for emphasis. *Scientific merit, as assessed by evaluation of all applications in the traditional NIH peer review system, will continue to be the principal factor considered in determining which approved grant proposals the NEI will fund.* However, additional measures will be taken by the Council and NEI staff to help fulfill the Plan's recommendations. These measures include:

- Designating some approved grant applications as having *High Program Relevance*, thereby placing them in a more favorable position for funding than would otherwise be the case.
- Encouraging the development of proposals for high quality *clinical research*, including clinical trials and other epidemiologic approaches.
- Encouraging *research training and career development* in the sciences related to vision, with particular emphasis on clinicians and other investigators who can help implement the priorities outlined in the Plan.
- Sponsoring *scientific workshops* in selected priority areas to encourage exchange of scientific information and techniques among vision scientists and between vision scientists and investigators in other fields. Workshops will be held in areas in which interdisciplinary interaction is considered especially important to advancing the field, such as in ocular immunology.
- Supporting *core grants* to help maintain institutional environments which foster high quality collaborative research and multidisciplinary approaches among investigators who already have NEI individual research grant support.
- Funding *specialized clinical research centers* to support a group of clinical studies which have a common focus on the etiology, pathogenesis, diagnosis, or treatment of human visual disorders.
- Providing for the maintenance and distribution of *special research resources*, such as laboratory animal breeding colonies and human donor tissue, as well as establishing special arrangements, such as consortium grants, to pool scarce resources in cooperative endeavors related to the priorities of this Plan.
- Selectively using *research contracts* or *cooperative agreements* to continue support of NEI-initiated multicenter clinical trials and for the procurement of special research resources.
- Using the NEI *intramural research program* to take advantage of the unique resources and environment of the NIH campus in Bethesda, Maryland, in carrying out the priorities of this Plan and to serve as a national resource for the training and career development of basic and clinical vision researchers.
- Encouraging the *transfer of scientific knowledge and the dissemination of information* to practitioners and the general public to help in achieving the NEI's long-range goal to improve the visual health of the American people through research.
- Participating in *international activities and agreements* that provide a knowledge base for worldwide efforts to prevent blindness, broaden the scope of vision research generally, and bring about better utilization of research resources in participating countries.

Each of these measures is discussed in greater detail in Chapter 3, "Implementation of Program Priorities."

Figure 2 represents schematically how the National Advisory Eye Council's vision research Plan interacts with the traditional system for dual level peer review of grant applications that has served NIH so well over the years. The diagram shows that the NEI and the Council continue to rely primarily on the peer review system for determining which grant applications will be approved and recommended for funding. The National Plan serves as an adjunct to the peer review process by first attempting to encourage the submission of grant applications for research in areas designated as Program Development Priorities, and second by providing a systematic basis for the funding actions of the Council and NEI staff.

The lower left-hand corner of the diagram indicates the development of the Plan by the Council and the NEI in conjunction with leading representatives of the vision research community. Next, the published Plan is widely disseminated to scientists, and other measures are taken to assure its implementation. In general, the scientific community as a whole is relied upon to respond voluntarily to the Plan's recommendations; there is no earmarking of funds or extensive use of contracting. Because leading representatives of the scientific community play a major role in the Plan's development, an overall positive response to its recommendations is expected.

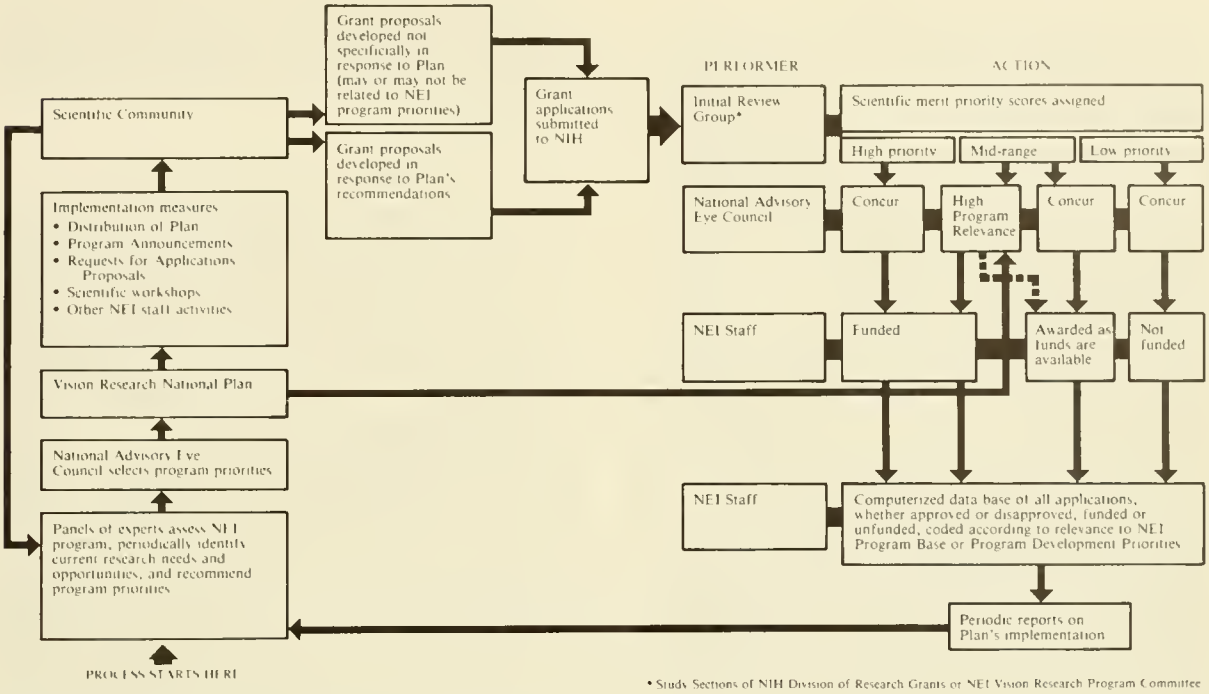


FIGURE 2. National Eye Institute Program Planning System. Both the NIH scientific merit priority scores and the program priorities established in the National Plan help determine which grant applications NEI will fund. All applications with high scientific merit priority scores are funded regardless of their relevance to program priorities. Some applications with mid-range scores and judged to be highly relevant to program priorities are singled out and placed in a better funding position than they would have been on the basis of the score alone.

The diagram depicts individual scientists as either responding intentionally to the Plan's recommendations or not. In either case, it is certain that many scientists will submit applications for research grants that coincide with the Plan's recommendations. All grant applications are processed through the traditional NIH dual level peer review system. The responsibilities of the initial review groups are to assess the scientific merit of an application and to judge the reasonableness of the budget proposed to carry out the project. The initial review group assigns a scientific merit (priority) score to approved applications; no score is assigned to disapproved applications. (For simplicity's sake, disapprovals are not shown on the diagram.)

The next level of review is the National Advisory Eye Council which examines all applications, whether approved or disapproved. The Council has the authority to return with comments an application to the initial review group for re-review. In practice the Council generally concurs with the initial review group's assessment. The applications referred by the Council to the NEI Director for consideration of funding that receive the best scientific merit scores will generally be paid; those with the poorest scores will not. For the group of applications with mid-range scores, some will be funded, some will not, depending on the availability of funds. Some applications that are not funded immediately may be held over to be paid later in the year. It must be stressed that the primary, but not only, factor that determines which applications are paid is the initial review group scientific merit score.

For those applications with mid-range scores, the margin between funded and unfunded may be only a few points. The Council does not have the authority to change scores, but it can recommend that a particular grant be given preferential consideration for payment. It does this by designating an application as having High Program Relevance, that is, having a high potential for fulfilling a program priority. For example, such a proposal may concern an innovative approach to an important disease problem for which little or no current support exists. In any case, even though the Council may designate an application as having High Program Relevance, it is for the NEI Director, acting on advice of NEI program staff who also consider the potential effect on overall program balance of funding the application, to make the final decision on whether the grant is paid or not. The Director may or may not, at his discretion, fund any grant the

Council recommends for approval, but he may not fund an application that has been disapproved.

In making its High Program Relevance recommendations the Council and staff could, if they wished, proceed on an ad hoc basis, guided by personal biases and opinions, perhaps even acting inconsistently from one meeting to another. We have chosen rather to be guided consistently by a carefully developed program Plan based on broad scientific input and supplemented by periodic data provided by NEI staff pertaining to the Plan's implementation. It is important to stress that to date at any given Council meeting only an average of three percent of all grant applications with mid-range scores have actually been designated as having High Program Relevance, although about five percent were initially considered for such action. However, if budget constraints increase, it is probable that the percentage of awards so designated may likewise increase. We believe this is a necessary and proper procedure for a program whose mandate is to improve the visual health of the American people.

We hope that this explanation of the High Program Relevance designation process will make clear that the Council has no intention of disrupting the time-honored, dual level NIH peer review system in which the scientific merit evaluations of an independent review body are conveyed to the Council for consideration and recommendation to the Director. We strongly affirm our support and belief in this unique review mechanism, as have Councils before us. In exercising the High Program Relevance option, albeit sparingly, we are in fact carrying out a charge given to all NIH senior advisory groups. We see the judicious exercise of this obligation as having a positive influence on the attainment of the scientific goals and objectives that vision research scientists themselves have helped establish.

NATIONAL EYE INSTITUTE PROGRAMS

All vision research conducted and supported by the NEI is classified into five major programs that encompass basic and applied research on a large number of often related eye and visual disorders that are the most important causes of visual deprivation and blindness in the United States. The five programs are Retinal and Choroidal Diseases; Corneal Diseases; Cataract; Glaucoma; and Strabismus, Amblyopia, and Visual Processing. Because of the importance of Visual Impairment and Its Rehabilitation, special consideration is given in the National Plan to this broad topic which has relevance to many of the diseases covered in the five NEI programs.

The Visual System

Before describing the NEI programs briefly and as a prelude to the Summary Panel Reports contained in Chapter 2, it is useful to review the major components of the human visual system. Labeled structures not described in this section are discussed either in the following program descriptions or in Chapter 2. The first time they are mentioned, they are printed in italics.

Each portion of the eye and visual pathways depicted in Figures 3, 4, and 5 performs a specific function. The optical elements of the eye, the *cornea* and the *lens*, focus images onto the *retina*, a thin, light-sensitive membrane lining the inside of the back of the eye. The *iris* regulates the amount of light falling on the retina by changing the size of the *pupil*. The two major functions of the *ciliary body* are to secrete *aqueous humor*, a clear fluid that nourishes the cornea and lens, and, by means of suspensory ligaments called *zonules*, to hold the lens in place and change its shape and thickness (a process known as accommodation) so that the eye can focus on objects at various distances. The *vitreous humor*, the clear gel that fills the center of the eye, helps maintain the eye's shape.

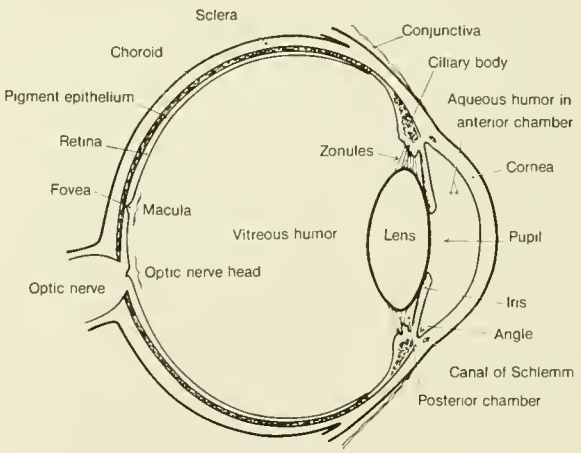


FIGURE 3. Cross section of the human eye.

The transmission of visual information through the retina is a complex process. The retina's photoreceptor cells, called rods and cones, convert incoming light to electrical signals which are further processed and integrated by an exquisitely organized cellular system. The ganglion cells, the output

cells of the retina, have been classified into functionally specialized types, each sensitive to different stimulus sizes, velocities, and locations in the visual

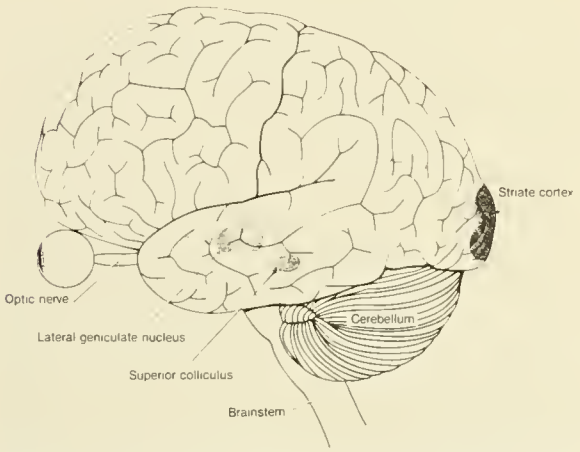


FIGURE 4. Lateral view of human brain, including interior visual pathway structures; lateral geniculate nucleus and superior colliculus.

field. Axons from the ganglion cells form the *optic nerve* and *optic tract*. These connect with the *lateral geniculate nucleus*, a group of cells in the thalamus of the brain. From there nerve impulses are sent to the striate area of the *visual cortex* at the back of the brain. The striate cortex is also a complex structure, divided into anatomically distinct layers and functionally separate columns of cells. Neurons in this area send axons forward to many other cells and back to many of the areas from which they receive input. Some retinal ganglion cell axons send branches into a region of the midbrain, the *superior colliculus*, which aids in orientation to objects or other visual stimuli through control of eye movements. Circuits of neurons in the *brainstem*, including their connections with the *cerebellum*, are also important parts of the eye movement system.

Clearly, the visual system is highly organized and complex; a major portion of the brain is directly and exclusively involved in the visual process. This is consistent with the very great sensory importance of sight.

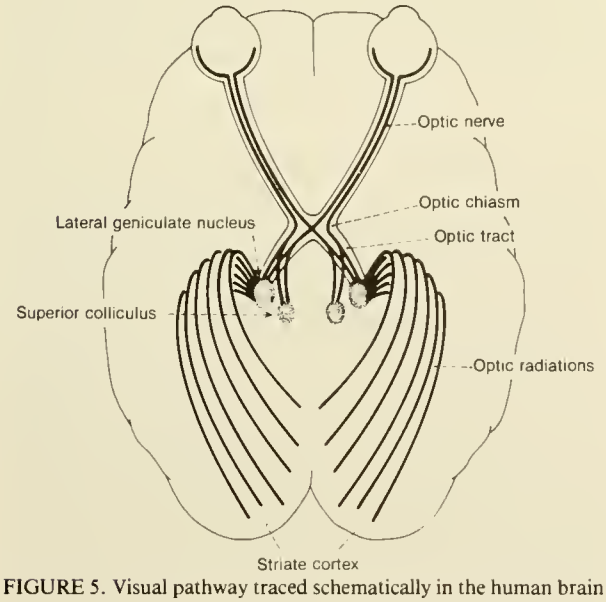


FIGURE 5. Visual pathway traced schematically in the human brain.

Retinal and Choroidal Diseases

Most blindness and visual disability in the United States is caused by disorders of the retina and the choroid, the underlying layer of blood vessels that nourishes the retina. Because of the proximity and interrelationship of these two structures, diseases affecting one usually involve the other. The most important disorders and diseases of the retina and choroid include diabetic retinopathy, aging-related maculopathy, retinitis pigmentosa, retinal detachment, uveitis (ocular inflammation), retinal tumors, and damage caused by environmental or toxic agents and drugs. Unfortunately, for most of these conditions, there is neither means of cure nor prevention. Progress against them depends on gaining new knowledge of the fundamental processes related to retinal and choroidal function and the development of new approaches to clinical diagnosis and treatment.

Corneal Diseases

Included within this program are basic and clinical research relevant to diseases of the cornea, the transparent structure at the front of the eye, and of the external ocular structures, including the conjunctiva and eyelids. Also included in the Corneal Diseases program is research on corneal transplantation and wound healing as well as contact lenses and surgical correction of myopia and other refractive errors. The leading causes of corneal blindness and impairment are herpes simplex and other infections, corneal swelling, and inherited and degenerative diseases. Corneal diseases occur frequently and are the leading cause of blindness worldwide. They are also, as a group, the most painful of eye disorders.

Cataract

A cataract is an opacity of the normally clear lens of the eye which interferes with vision. Opacities of the lens may be a consequence of aging, diabetes or other metabolic disorders, or toxic and environmental agents, or they may be inherited or congenital. Although the removal of a cataractous lens today is a highly successful surgical procedure, cataracts remain among the leading causes of blindness in the United States and throughout the world. For this reason, the National Eye Institute emphasizes basic and clinical research aimed at the prevention and nonsurgical treatment of cataract, although the evaluation of new diagnostic and surgical techniques is also a prime concern. Also included in this program is research on dislocated lenses.

Glaucoma

This disease is typically characterized by an elevation of pressure within the eye caused by a build-up of the aqueous humor, a fluid produced by the ciliary body to nourish the cornea and lens, which normally drains from the eye through outflow channels. Obstruction of aqueous outflow is followed by damage to the optic nerve and subsequent loss of vision. Some glaucoma patients have optic nerve damage accompanied by what is considered normal intraocular pressure, while in others elevations of intraocular pressure to the same level can result in varying degrees of damage to the eye and its susceptible tissues. Although glaucoma is mostly a disease of the aging, it may occur at any age or at birth. Glaucoma can occur as a primary disorder or occur secondary to other ocular or systemic conditions. Research in this program encompasses both basic research on the structures and mechanisms involved in glaucoma as well as clinical research on prevention, diagnosis, and treatment.

Strabismus, Amblyopia, and Visual Processing

This program, formerly called Sensory and Motor Disorders of Vision, encompasses a broad range of basic and clinical studies concerned with the structure and function of the neural pathways from the retina to the brain, the central processing of visual information, visual perception, optical properties of the eye, functioning of the pupil, control of the ocular muscles, and refraction. A large number of congenital, developmental, and degenerative abnormalities affect the visual sensorimotor system, but three disorders are of primary concern: strabismus, amblyopia, and nystagmus. These are frequent causes of visual impairment among children which may persist throughout life. Of particular interest are studies of the normal development of visual capacity in the infant and of the effects of early sensory deprivation on the development of visual function.

Visual Impairment and Its Rehabilitation

Each of the preceding programs encompasses research on diseases and disorders that can produce blindness and a broad range of lesser degrees of visual impairment that may be no less disabling. Some people with impaired vision can get along quite well with simple optical and mechanical aids. Others require more specialized and sophisticated devices. Only in recent years has the extraordinary diversity of visual characteristics and rehabilitative needs within this group of people begun to be appreciated. Although the NEI has no separate program for research in this field, the necessity to address these needs is an integral part of the goals and objectives of each of the five disease-oriented programs. Thus, projects in visual impairment and its rehabilitation are funded out of the NEI program to which they most closely relate. If a project does not focus on a specific disease, it will probably be funded within the Strabismus, Amblyopia, and Visual Processing program. Because of increasing awareness of and interest in the problem of visual impairment and its rehabilitation among professionals and the public alike, the Council established a special program planning Panel to consider research needs, opportunities, and priorities in this field. This includes research aimed at enhancing the remaining vision of individuals, evaluating new and existing optical aids, studying video magnification or image enhancement systems, and other techniques and strategies aimed at improving visual capabilities and performance.

Subprograms

For purposes of program analysis, evaluation, and planning, each of the five NEI programs is further divided into subprograms that represent the principal areas of research encompassed. During each planning cycle the program Panels, working with the NEI staff and Council, carefully consider the program structures used in the previous National Plan to determine if they remain consistent with the present state of scientific knowledge and interest and if they provide a suitable framework for the Panel's current assessment and report. In the course of developing the 1983–1987 National Plan, the Panels made a number of changes in the program structures used in the 1978–1982 National Plan.

One reason for change was the Panels' desire to convey the importance of maintaining a balance between basic and applied research and to demonstrate the essential relationships between both ap-

proaches in the conquest of blinding and disabling eye diseases. Another reason was to emphasize more clearly the number and variety of disease and research problems with which a program is concerned. In such cases the Panel members hoped that a more specific delineation of these problems would help attract researchers to them.

A third reason for restructuring a program was the need to achieve a framework for planning that stresses the differences within a particular group of closely related diseases. For instance, some NEI programs encompass disorders, such as cataracts, which, although they affect a single ocular tissue and may be superficially similar in appearance, differ markedly as to cause, underlying mechanisms, clinical features, and therapeutic approach.

Among the five programs, there are naturally many areas of mutual and even overlapping concerns. For example, the ocular effects of diabetes are of interest in both the Retinal and Choroidal Diseases program and the Cataract program. Congenital and developmental eye disorders are common to all five programs. Because of these shared problems and concerns, progress in one area of vision research may well lead to advances in another. This indicates the need for improved communication among scientists in the various specialized fields of vision research and for increased collaboration among such individuals in investigations of mutual interest. The Council hopes that this latest National Plan will help facilitate such interactions.

The following is an outline of the NEI program/subprogram structure upon which the 1983–1987 National Plan is constructed.

Retinal and Choroidal Diseases

Vascular, Inflammatory, and Neoplastic Disorders of the Retina and Choroid

1. Diabetic Retinopathy, Sickle Cell Retinopathy, and Other Vascular Abnormalities
2. Inflammatory Disorders
3. Tumors

Degenerative Disorders of the Retina

4. Developmental and Hereditary Disorders
5. Macular Degeneration
6. Retinal Detachment and Vitreous Disorders
7. Toxic and Environmental Disorders

Fundamental Processes and Retinal Disorders

8. Retinal Pigment Epithelium
9. Photoreceptors, Visual Pigments, and Phototransduction
10. Retinal Organization, Neurotransmission, and Adaptation
11. Glial Cells and the Retinal Microenvironment
12. Rescue and Regeneration of Neurons in the Optic Nerve and Retina

Related Areas of Research Opportunity and Need

13. Noninvasive Techniques in the Study of Retinal Disorders
14. Tissue Acquisition and Distribution: Human Donor Eyes and Animal Models

Corneal Diseases

1. External Ocular Infections and Inflammatory Diseases
2. Ocular Surface Problems
3. Refractive Problems and Contact Lenses
4. Corneal Edema, Endothelial Dysfunction, Dystrophies, and Inherited Diseases
5. Corneal Transplantation and Wound Healing

Cataract

1. The Normal Lens
2. Epidemiology of Cataract
3. Senile Cataract
4. Diabetic and Metabolic Cataract
5. Nongenetic Congenital and Genetic Cataracts and Dislocated Lenses
6. Cataract Induced by Environmental and Toxic Effects
7. Treatment of Cataract and Correction of Aphakia

Glaucoma

Primary Open-Angle Glaucoma

1. Etiology, Epidemiology, Management, and Therapy
2. Aqueous Humor Dynamics: Inflow
3. Aqueous Humor Dynamics: Outflow
4. The Optic Nerve

Other Glaucomas

5. Angle-Closure Glaucoma
6. Developmental, Congenital, and Infantile Glaucomas
7. Secondary Glaucomas

Strabismus, Amblyopia, and Visual Processing

1. **Visual Processing and Amblyopia**
   a. Normal and Abnormal Development
      (1) Molecular
      (2) Cell and Systems
      (3) Behavior
   b. Structure and Function
      (1) Molecular
      (2) Cell and Systems
      (3) Behavior

c. Disorders
(1) Amblyopia
(2) Sensory Neuro-Ophthalmic Disorders

2. **Ocular Motility and Strabismus**
a. Normal and Abnormal Development
b. Structure and Function
(1) Conjugate Eye Movements
(2) Vergence and Accommodation
(3) Muscle Structure and Physiology
c. Disorders
(1) Strabismus
(2) Motor Neuro-Ophthalmic Disorders

3. **Optics and Refractive Errors, Including Myopia**
a. Optics and Refractive Errors, Including Myopia

EXTENT OF THE PROBLEM

Any determination of the health research needs and priorities of the Nation must begin with an assessment of the magnitude of the disease problem being addressed. Therefore, in preparing this Plan the Council sought reliable statistics on the extent and costs of eye diseases and blindness. The sources that have been used are *Vision Problems in the U.S.*, a statistical analysis of currently available data from a variety of sources prepared by the National Society to Prevent Blindness, other published and unpublished data from the Public Health Service's National Center for Health Statistics, and material presented in previous NAEC plans that has been updated.

The major source of data regarding blindness continues to be the Model Reporting Area for Blindness Statistics (MRA), which was discontinued in 1970. Although there is strong evidence that the MRA data considerably underestimated the incidence and prevalence of blindness, there is still no better source for blindness data. The National Society to Prevent Blindness used the 1970 MRA rates to estimate that in 1978 there were 498,000 legally blind Americans.

Table 1 indicates the extent of the problem of visual disorders in the United States. Data on the

TABLE 1. The Extent of the Problem of Visual Disorders, United States

NEI Program	No. and Percent Distribution of Visual Impairment[1]		New Cases of Legal Blindness[2]	Prevalence of Legal Blindness[3]	Annual Incidence of Eye Diseases[4]		Office Visits for Medical Eye Care[5]	Persons Hospitalized for an Eye Disorder[6]
	No. cases	%			No. cases	%		
Retinal and Choroidal Diseases	413,000	3.6	18,950	192,500	707,000	11.0	2,130,000	58,000
Corneal Diseases	4,219,000	36.9	1,250	24,700	4,280,000	66.9	7,840,000	81,000
Cataract	3,558,000	31.2	6,150	71,550	694,000	10.9	3,751,000	332,000
Glaucoma	889,000	7.8	5,500	67,150	273,000	4.2	2,573,000	36,000
Strabismus, Amblyopia, and Visual Processing	—	—	5,400	79,750	443,000	6.9	10,418,000	68,000
Other/Multiple/ Undetermined	2,337,000	20.5	9,350	62,350	—	—	7,010,000	76,000
Total	**11,415,000**	**100.0**	**46,600**	**498,000**	**6,399,000**	**100.0**	**33,722,000**	**651,000**

[1] Visual impairment refers to chronic or permanent defects resulting from disease, injury, or congenital malformation as reported in the National Center for Health Statistics' (NCHS) Health Interview Survey, by etiology for 1977.

[2] Estimated distribution for 1978 according to site and type of affection by National Society to Prevent Blindness based on unpublished Model Reporting Area data on new additions to the blindness registers in participating states, 1969–1970 average.

[3] Estimated distribution for 1978 according to site and type of affection by National Society to Prevent Blindness based on unpublished Model Reporting Area register data as of December 31, 1970.

[4] Developed from *Vision Problems in the U.S.*, published by the National Society to Prevent Blindness. Based on annual number of visits for eye care by new patients and previous patients with a new problem. Estimates for 1976 from the NCHS National Ambulatory Medical Care Survey, unpublished data.

[5] Estimates for 1976 from NCHS National Ambulatory Medical Care Survey, unpublished data. Includes only eye conditions due to those disease entities which were reported by ophthalmologists.

[6] Persons discharged from non-Federal short-stay hospitals with an eye disorder as the principal or first-listed diagnosis. Estimates for 1976 from the NCHS Hospital Discharge Survey, unpublished data.

distribution of visual impairment, new cases and prevalence of legal blindness, annual incidence of eye diseases, office visits for medical eye care, and persons hospitalized for an eye disorder are listed for each of the five NEI programs. Table 2 shows the major causes of legal blindness in the United States in 1978.

TABLE 2. Major Causes of Legal Blindness, United States, 1978

	Existing Cases (Prevalence)[1]	New Cases (Incidence)[2]
Glaucoma other than congenital	62,100	5,350
Macular degeneration	58,250	7,850
Senile cataract	41,500	4,550
Optic nerve atrophy	34,500	2,000
Diabetic retinopathy	32,650	4,700
Uveitis including chorioretinitis	30,450	1,650
Retinitis pigmentosa	23,250	1,450
Myopia	19,850	1,250
Retrolental fibroplasia	12,600	150
Detachment of retina	8,300	650

[1] Estimated distribution according to site and type of affection by National Society to Prevent Blindness based on unpublished Model Reporting Area register data as of December 31, 1970.

[2] Estimated distribution according to site and type of affection by National Society to Prevent Blindness based on unpublished Model Reporting Area data on new additions to the registers, 1969–1970 average.

Other data show that:

- Over 10 million people—about 1 of every 20 in the United States—suffer from significant impairment of vision which cannot be further improved by corrective lenses.
- Of these, 1.5 million have such severe impairment that they are unable to read ordinary newsprint, even with glasses.
- Of those severely impaired, approximately 500,000 are legally blind.
- Approximately 47,000 new cases of legal blindness occur each year.
- Each year, more than 1.1 million people are hospitalized for an eye disorder.
- Approximately 2.5 million eye injuries occur annually, almost 1 million of which cause permanent visual impairment.
- Eye conditions necessitate almost 34 million visits for professional care or treatment each year.
- Each year over 1,050,000 eye operations are performed.
- The economic costs of visual disorders and disabilities for 1981 have been estimated to be $7.9 billion in direct costs alone. An estimated $6.2 billion in indirect costs (days lost from work, etc.) and noneconomic costs, when added to the direct costs, bring into focus the truly staggering consequences of eye-related problems.

To obtain reliable data on the prevalence of major eye disorders in a defined population, the NEI sponsored the Framingham Eye Study (FES) from 1973 to 1975. Although it included 2,675 mostly white residents aged 52 to 85 in a small geographic area (Framingham, Massachusetts), the FES had a carefully designed research protocol and good quality control. This study measured the prevalence of senile cataract (15.5 percent), aging-related maculopathy (senile macular degeneration) (8.8 percent), diabetic retinopathy (2.1 percent), and glaucoma (2.5 percent) in this population.

An example of how vision research can have an impact on these statistics by preventing blindness and reducing costs is provided by a study of the safety and efficacy of laser treatment of diabetic retinopathy. As a result of findings from the NEI-sponsored Diabetic Retinopathy Study, a five-year multicenter clinical trial costing approximately $5 million, it is estimated that laser treatment will be able to spare 22,250 people blindness and thereby save $4.4 billion over a ten-year period.

The net saving to society as a result of a nationwide clinical trial of laser treatment for one form of aging-related maculopathy will be at least $250 million for each year that the results from the study are fully applied. This is a conservative estimate, based on the assumption that laser treatment will delay by two years (the length of the study) the onset of blindness in about 13,000 people who have this disease in both eyes and who will almost certainly become blind within the next year if they do not receive this treatment. It is possible that additional follow-up will show that this treatment postpones blindness for a longer period of time or prevents it altogether. If that is the case, the annual savings will be several times greater than $250 million.

Recent research results from animal studies have indicated that it may be possible to develop drugs that will slow cataract formation in humans, thus eliminating the need for 180,000 cataract operations per year. If by using such drugs it becomes possible to delay surgery for cataract by ten years, the net annual savings that will accrue will be $270 million.

In recognition of the unavailability of truly sound data on the prevalence of visual acuity impairment

and its causes in the United States, the National Eye Institute is organizing one of the most comprehensive visual health surveys ever undertaken, the nationwide Visual Acuity Impairment Survey. This survey will be conducted in 1984 in cooperation with the National Center for Health Statistics and the Bureau of the Census. Samples of the adult U.S. population, age 25 and older, residing in 15 large metropolitan areas will be studied. The survey will investigate how the risk of having central distance visual acuity impairment varies according to demographic, social, personal, environmental, biologic, and genetic factors.

Visual acuity will be determined in the home during the course of an interview survey of general health, which will describe the population among which the visually impaired persons are found by age, sex, and other characteristics. Persons who do not meet the study's criteria for visual acuity will be invited to attend a local clinic for a comprehensive ophthalmological examination. As a check on the effectiveness of the screening techniques, a sample of people with better vision will also receive the comprehensive examination. An important aspect of the study is that those persons who do not have impaired vision will provide population-based controls for studies of risk factors for each of the diseases that are found to be major causes of visual impairment.

SUPPORT FOR VISION RESEARCH

The National Advisory Eye Council and the planning Panels reviewed a substantial amount of data on the support of vision research in the United States as background information for assessing current needs and opportunities in this field, identifying priorities for future funding, and addressing major issues relating to the National Eye Institute's program. In publishing these data, the Council reaffirms its belief that a periodic survey of vision research projects funded not only by the NEI but by other government and private organizations provides essential information that can be used to assess gaps in support as well as to identify research areas for which current funding appears to be adequate.

The next three tables provide summary information on support for vision research by the NEI in FY 1981 and other organizations in the United States during FY 1980. The primary source of information on research supported by the Federal Government was the Smithsonian Science Information Exchange (SSIE). Each organization identified by the SSIE to have funded vision research in FY 1980 was contacted and asked to verify or correct the SSIE-supplied abstracts of the projects they supported. National philanthropic organizations known to support vision research were also contacted and asked to supply a list of projects they funded in FY 1980. Each abstract was carefully reviewed to determine the relevance of the project to the mission and program goals of the National Eye Institute.

Not included in this compilation is research support provided by state and local governments, corporations, and the private resources of individual investigators. The Council recognizes that funding from these sources may be substantial, but reliable data concerning them are virtually impossible to obtain.

Vision research support is listed for the following categories: National Eye Institute; other Institutes of the National Institutes of Health; other components of the Department of Health and Human Services; other agencies of the Federal Government; and private, philanthropic, and voluntary health organizations.

The contribution to vision research that is made by private organizations cannot be measured by dollars alone. Besides giving support and encouragement to promising young investigators, these organizations are often able to provide funding for facilities construction, equipment, and other vital research resources that cannot always be obtained from public funding agencies. They also frequently provide timely funding for the development of innovative techniques or for exploiting unusual opportunities that may otherwise have been lost in the course of the necessarily longer review process required for government research grant applications.

Volume Three of this National Plan presents detailed lists of research projects reviewed by the Council and its consultants. These lists are organized under three major headings: (1) NEI Program Data, (2) Research of *direct relevance* to the NEI program sponsored by other organizations, and (3) research of *indirect relevance* to the NEI program sponsored by other organizations.

Projects considered *directly relevant* to the NEI program are defined as those whose primary objective, as determined by a review of their abstracts, is to learn something about either the normal structure or function of the visual system or about the etiology, pathogenesis, prevention, diagnosis, or treatment of visual disorders. That is, they are primarily concerned with gaining new knowledge and understanding of the normal functioning of the eye and visual system, the pathology of visual disorders, and/or the sciences underlying vision. Within each of the five NEI programs to which these projects correspond, there is a list of the grants, contracts, and intramural projects of all

other components of NIH and DHHS, all other Federal funding, and support by private, philanthropic, and voluntary organizations.

The fact that in addition to NEI, other components of NIH, the Department of Health and Human Services, and other Federal departments provide support for vision research that is directly relevant to the mission of the NEI demonstrates the variety of diseases and scientific problems with which the discipline is concerned. In some instances this support is for projects that include the eye among a number of organ systems in which a particular disease is being studied. In such cases, an attempt has been made to identify that portion of funding limited to the eye alone, although this is frequently difficult to do. That another Institute or agency other than the NEI supports any given project indicates either that the primary focus of the research is oriented to the mission of that organization or that NEI funds were not available to support the project at the time it was approved, but another organization, whose mission also encompassed the project, was interested in and able to fund it.

Projects considered to be of *indirect relevance* to the NEI program are those in which the visual system or its components are only minor or incidental elements or in which the eye is merely used as a test system or tool to gain information on topics other than vision. In this category the vision-related portion of the listed projects may be incidental and involve ocular tissues or visual function only secondarily, if at all. Such projects are listed in Volume Three because they relate to vision research in its broadest sense and may be of interest to the readers of this report. Funding in this category, however, is not included in Tables 3, 4, and 5. As in the preceding category, the projects are supported by other components of NIH and DHHS, by other agencies of the Federal Government, and by private, philanthropic, and voluntary organizations. Again, although they are grouped according to their relationship to the five NEI programs, the projects in this category bear only indirectly upon the mission of the NEI.

Table 3 summarizes by major funding source the amount spent for vision research with direct relevance to the NEI program by organizations in the United States. Only those projects whose primary objective was to learn more about the structure or function of the visual system in health and disease were included.

TABLE 3. Summary of Vision Research Funding, FY 1981*

	Amount of Funding	Percent of Funds
Federal Government		
National Eye Institute	$117,983,000	85
National Institutes of Health (Exclusive of NEI)	10,559,518	7
Department of Health and Human Services (Exclusive of NIH)	702,527	1
Other Federal Support	6,845,275	5
National Private, Philanthropic, and Voluntary Health Organizations	2,357,125	2
Total	**$138,447,445**	**100**

*Funding for organizations other than the National Eye Institute is FY 1980.

Table 4 displays in greater detail, according to the individual government and private agencies and organizations that provide support to vision research, the totals that are summarized in Table 3.

Table 5 categorizes the information shown in Tables 3 and 4 according to the five research programs of the NEI. A sixth category (Multiprogram and Other) has been added for vision research funds not clearly applicable to an NEI extramural program.

Table 6 presents the NEI's appropriation history. Although the NEI appropriation has increased almost fivefold over the past 12 years, its increase has been little more than double in terms of constant dollars.

Table 7 is a historical analysis of the NEI budget by its program components. Comparable data for fiscal years before 1974 are not available because the NEI budget was not prepared in this form until that year. These programs were established in 1974 by grouping NEI's existing grants according to their relevance to one of the five major types of related visual disorders. Since then, Congress has appropriated funds annually by program, although flexibility is allowed under certain conditions for reprogram-

TABLE 4. Sources of Vision Research Funding with Direct Relevance to the NEI Program, FY 1980.

Supporting Organization	Total Awarded
National Institutes of Health (Exclusive of NEI)	
Fogarty International Center	$267,051
National Cancer Institute	440,509
National Heart, Lung, and Blood Institute	700,911
National Institute of Allergy and Infectious Diseases	1,591,997
National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases	1,226,419
National Institute of Child Health and Human Development	1,246,848
National Institute of Dental Research	117,144
National Institute of Environmental Health Sciences	99,555
National Institute of General Medical Sciences	527,752
National Institute of Neurological and Communicative Disorders and Stroke	4,021,388
National Institute on Aging	255,334
National Library of Medicine	64,610
Subtotal	**$10,559,518**
Department of Health and Human Services (Exclusive of NIH)	
Alcohol, Drug Abuse, and Mental Health Administration	498,807
Bureau of Radiological Health	*
Food and Drug Administration	94,759
Health Services Administration	5,000
National Institute for Occupational Safety and Health	53,520
National Institute on Drug Abuse	50,441
Subtotal	**$702,527**
Other Federal Departments	
Department of Agriculture	470,402
Department of Defense, Air Force	1,091,626
Department of Defense, Army	1,516,785
Department of Defense, Navy	263,000
Department of Energy	33,320
Environmental Protection Agency	40,000
National Aeronautics and Space Administration	30,000
National Institute of Handicapped Research	797,481
National Science Foundation	2,601,161
Uniformed Services University of the Health Sciences	1,500
Veterans Administration	*
Subtotal	**$6,845,275**
National Philanthropic and Voluntary Agencies	
American Cancer Society, Inc.	40,000
Fight for Sight, Inc.	524,545
Juvenile Diabetes Foundation	39,166
National Multiple Sclerosis Society	14,000
National Society to Prevent Blindness	79,542
Research to Prevent Blindness, Inc.	804,250
Retinitis Pigmentosa Foundation	755,622
Spencer Foundation	50,000
The Seeing Eye, Inc.	50,000
Subtotal	**2,357,125**
Total	**$20,464,445**

*Support provided, but total amount of funding is unknown.

TABLE 5. United States Vision Research Support by National Eye Institute Program, FY 1981[1]

	Retina	Cornea	Cataract	Glaucoma	Strabismus	Multiprogram and Other[3]	Total Awarded
Federal Government							
National Eye Institute	42,045,003[2]	16,961,273	9,737,034	9,382,426	24,329,230[2]	15,528,034	117,983,000
National Institutes of Health (Exclusive of NEI)	3,299,128	1,955,770	425,638	—	4,517,737	361,245	10,559,518
Department of Health and Human Services (Exclusive of NIH)	53,520	—	5,000	145,200	393,675	105,132	702,527
Other Federal Support	790,150	562,408	120,000	26,366	4,548,870	797,481	6,845,275
National Private, Philanthropic, and Voluntary Health Organizations	1,184,877	254,484	104,361	144,033	200,620	468,750	2,357,125
Total	**47,372,678**	**19,733,935**	**10,392,033**	**9,698,025**	**33,990,132**	**17,260,642**	**138,447,445**

[1] Funding for organizations other than the National Eye Institute is FY 1980.
[2] Includes Visual Impairment and Its Rehabilitation.
[3] Includes Direct Operations.

TABLE 6. National Eye Institute Appropriation History, FY 1970–1981

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation	Appropriation in Constant Dollars*
1970	$23,685	$23,685	$25,000	$24,343	($24,343)
1971	25,686	30,986	30,986	30,032	(28,383)
1972	32,639	36,022	40,187	37,133	(33,432)
1973	37,384	38,562	45,000	38,562	(33,135)
1974	32,092	36,631	46,631	41,166	(33,257)
1975	39,947	38,878	50,000	44,133	(32,212)
1976	39,201	42,608	50,000	50,212	(34,102)
1977	46,950	56,270	70,000	64,000	(40,257)
1978	65,436	85,400	75,352	85,400	(49,997)
1979	86,428	100,549	100,459	105,192	(56,897)
1980	104,462	107,528	113,000	112,989	(56,018)
1981	116,046	117,635	117,884	117,983	(53,043)

* The following price deflators were developed by the Division of Program Analysis, NIH, to compute constant dollars:

1970 — 100.00	1973 — 116.38	1976 — 147.24	1979 — 184.88
1971 — 105.81	1974 — 123.78	1977 — 158.98	1980 — 201.70
1972 — 111.07	1975 — 137.01	1978 — 170.81	1981 — 222.43

TABLE 7. NEI Obligations by Program, FY 1974–1981 (Dollars in Thousands)

	FY 1974	FY 1975	FY 1976	Transition Quarter	FY 1977	FY 1978	FY 1979	FY 1980	FY 1981
Extramural Research									
Retinal and Choroidal Diseases	$12,402	$14,092	$16,215	$3,515	$23,125	$31,132	$40,055	$41,241	$42,374
Corneal Diseases	6,024	6,596	6,890	922	7,586	9,958	13,430	15,071	16,811
Cataract	3,243	3,445	4,282	543	5,524	6,946	9,378	8,842	9,723
Glaucoma	5,290	5,012	6,561	774	7,692	8,912	10,855	10,255	9,977
Strabismus, Amblyopia, and Visual Processing	7,502	7,459	8,524	1,855	10,259	17,425	19,240	20,235	23,168
Total Extramural	**$34,461**	**$36,604**	**$42,472**	**$7,609**	**$54,186**	**$74,373**	**$92,958**	**$95,644**	**$102,053**
Direct Operations									
Intramural Laboratory and Clinical Research	2,325	2,683	2,535	590	3,380	4,150	4,562	5,359	6,418
NIH Management Fund[1]	1,998	2,217	2,558	667	3,231	3,299	3,554	4,016	4,543
Subtotal	**$4,323**	**$4,900**	**$5,093**	**$1,257**	**$6,611**	**$7,449**	**$8,116**	**$9,375**	**$10,961**
Biometry, Epidemiology, and Field Studies	414	410	339	100	476	487	550	756	685
NIH Management Fund[1]	61	77	72	4	11	0	0	0	0
Subtotal	**$475**	**$487**	**$411**	**$104**	**$487**	**$487**	**$550**	**$756**	**$685**
Research Management and Program Services	1,360	1,545	1,652	384	2,032	2,334	2,575	2,941	3,024
NIH Management Fund[2]	547	597	584	165	684	757	993	1,273	1,260
Subtotal	**$1,907**	**2,142**	**$2,236**	**$549**	**$2,716**	**$3,091**	**$3,568**	**$4,214**	**$4,284**
Total Direct Operations	**$6,705**	**$7,529**	**$7,740**	**$1,910**	**$9,814**	**$11,027**	**$12,234**	**$14,345**	**$15,930**
GRAND TOTAL	**$41,166**	**$44,133**	**$50,212**	**$9,519**	**$64,000**	**$85,400**	**$105,192**	**$109,989[3]**	**$117,983**

[1] These portions of the NIH Management Fund are assessments based on the central NIH services provided to NIH direct research activities conducted at the NIH campus in Bethesda, Maryland. These services include operation of the NIH Clinical Center, engineering services, utilities, computer services, and other research services.

[2] This portion of the NIH Management Fund is an assessment based on central NIH services provided for the general management and program direction activities of the NEI. These services include central NIH receipt and review of research grants, centralized NIH financial management and other administrative services.

[3] Excludes $3,000,000 appropriated for construction grants in FY 1980 and obligated in FY 1982.

is allowed under certain conditions for reprogramming during the year should it be necessary to do so. The programs listed in this table include all research grant, fellowship, and contract funds.

Table 8 displays historical data on applications for NEI individual research project grants (R01). Variations in the percent funded of all applications approved from year to year derive both from the number of applications received and recommended for approval and the amount of funds available in any given year.

Table 9 presents the number of individual research project grants (R01) supported by the NEI for each fiscal year since 1970. The number of grants supported by the NEI over this period has grown by more than 250 percent.

TABLE 8. National Eye Institute Competing Research Grant Applications History: Reviewed, Approved, and Percent Funded, FY 1971-1981

Year	Received and Reviewed	Recommended for Approval After Scientific Review	Approved and Funded	Recommended for Approval But Not Funded	Percent Funded of All Applications Approved
1971	227	183	119	64	65
1972	332	260	139	121	53
1973	391	319	154*	165	48
1974	382	335	175	160	52
1975	318	274	200	74	73
1976	349	297	199	98	67
1977	515	428	238	190	56
1978	734	608	390	218	64
1979	626	535	344	191	64
1980	578	476	234	242	49
1981	689	608	332	276	55

*Includes projects supported by impounded funds released in FY 1974 (15 months).

TABLE 9. Number of Individual Research Project Grants (R01) Supported by the National Eye Institute, FY 1970-1981

Year	Number of Projects
1970	353
1971	411
1972	421
1973	405
1974	444
1975	511
1976	579
1977	691
1978	759
1979	868
1980	892
1981	889

NOTES

1. Legal blindness is defined as visual acuity of 20/200 or poorer in the better eye, even when wearing eyeglasses or contact lenses, or a field of vision no greater than 20 degrees in its widest diameter.
2. The term used in the National Plan to replace the more common but misleading designation "senile macular degeneration."
3. Vision Research Program Planning: Report of the National Advisory Eye Council, Vision Research Program Planning Committee. US DHEW Publ Nos (NIH) 75-664 and 665, 1975.
4. Vision Research—A National Plan: 1978-1982, The 1977 Report of the National Advisory Eye Council. US DHEW Publ Nos (NIH) 78-1258, 1259, and 1260, 1977.

2

SUMMARY PANEL REPORTS

THE 1983-1987 NATIONAL PLAN is primarily based upon reports prepared by six Panels of scientists, one Panel for each of the National Eye Institute's five research programs—Retinal and Choroidal Diseases; Corneal Diseases; Cataract; Glaucoma; and Strabismus, Amblyopia, and Visual Processing—plus a special Panel to consider research needs in the field of Visual Impairment and Its Rehabilitation. These Panel reports constitute the six sections of Volume Two of the Plan.

Each Panel report follows a standard format designed to convey the program evaluation and planning process the Panels used in making their assessment and recommendations for NEI program development. This format is used in documenting the appraisal of each subprogram and, in some cases, of subsidiary research areas within a subprogram. This chapter summarizes each of these Panel reports, highlighting their major sections as follows:

Introduction. Description of the disease problems encompassed by the program and their public health impact, the research areas included in the program, and the program's organization.

Program Goals. Broad, general statements of what, over the long run, the program aims to achieve in solving the disease problems it addresses. (In the full Panel reports, short-term goals, called Objectives, are also defined for each subprogram and area.)

Current Support. Summary analysis of FY 1981 funding by NEI and of FY 1980 support by other public and private organizations for research related to the NEI program's goals.

Recent Accomplishments. Highlights of research results over the past five years that have helped fulfill the program goals.

Research Needs and Opportunities. Summary of important current research problems and promising approaches to their solution.

Training and Manpower Needs. Discussion of specific kinds of manpower needed to carry out research priorities.

Highlights of Program Development Priorities. A summary of the existing or new research areas that should be emphasized over the five-year period covered by the Plan. (In the unabridged Volume Two Panel reports, the Program Base, which consists of established areas of research the Panels recommend receive essentially level support during the five-year period of the Plan, is also described.)

Resource Tables. Tables summarizing by subprogram the Panels' specific recommendations for program development. For each subprogram, the tables show the number and cost of projects supported in FY 1981, the Panels' recommendation for either growth or maintenance, and the net result expected by FY 1983. The total number of grants for FY 1983 for each subprogram indicated in the third column is the estimated sum of new and continuing awards to be made in that year along with an estimate of their cost.

The actual number of grants that will be funded in these areas may of course be either more or less than these projections indicate, depending on the quality, kind, number, and costs of the grant applications NEI receives and the actual availability of funds. Concerning funding, it must be emphasized that the six Panels' dollar estimates for FY 1983 do not necessarily indicate what the actual National Eye Institute extramural research budget will be for that year. However, because the Panels' estimates are based upon detailed documentation of projected research needs and costs, it is hoped that those in the Executive and Legislative branches of the Government who make the final decisions concern-

ing the NEI budget will use them in making informed judgments about the resources required for the support of vision research. In making these estimates the Panels took into account the following factors for each category of research considered:

- Degree of relevance to the program's goals and objectives;
- Current level of support by NEI and other organizations;
- Recent research accomplishments;
- Potential for future development;
- Availability of trained manpower; and
- Likelihood of significant progress over the next three to five years.

(In addition, more detailed tables, listing current and projected support within each subprogram, accompany each Panel report in *Volume Two*. In these tables, the Panels' recommendations are categorized under two major headings: *Program Base* and *Program Development Priorities*.)

Following the Panel report summaries, at the end of this chapter, is a table that aggregates the Resource Tables for each program and translates them into the Council's planning budget for the years FY 1983 to FY 1985. Because of increasing uncertainties in the annual Federal budget, the Council has not recommended a budget for the final two years covered by the Plan, but intends to revise and extend its estimates periodically. The purpose of this budget is to show what resources the Council estimates would be required to carry out this research Plan in its entirety during those three years. The Council budget is therefore intended as a guide to the NEI staff and those at higher levels of government for use in formulating NEI's actual budget during those years.

RETINAL AND CHOROIDAL DISEASES

Introduction

The retina is a thin, transparent, light-sensitive membrane that lines the inside of the back of the eye. The retina contains a mosaic of photoreceptor cells (the rods and cones) which converts the entering light, focused sharply by the cornea and lens, to electrical signals. These signals are transmitted through an exquisitely organized system of nerve cells which encodes the visual message and transmits it to the brain via the optic nerve.

If damaged, the retina is incapable of regenerating. Moreover, the normal functioning and very survival of the retinal cells depend on a carefully controlled environment and a continuous supply of oxygen and nutrients supplied by two systems of blood vessels, one within the retina, the other in the highly vascular choroid, the tissue lying immediately underneath the retina. Damage to the retina, interruption in its blood supply, or injury to the tissues with which it interacts, such as the pigment epithelium (a single cell layer between the retina and choroid that controls many nutritive exchanges between the blood and the retina), can lead to loss or severe impairment of vision. Unfortunately, the retina is susceptible to injury in numerous ways, including damage from systemic disorders such as diabetes and sickle cell anemia, infection and inflammation, circulatory failure, hereditary factors, aging, trauma, and toxic and environmental factors. Each may have devastating consequences for vision and the conduct of a normal, productive life.

Over 750,000 Americans with a retinal disorder suffer from visual impairment that is so severe they are unable to read ordinary newsprint, even with glasses. Of these, 200,000 are legally blind, making this group of diseases the leading cause of blindness in the United States. In fact, one of these diseases, diabetic retinopathy, is the leading cause of new cases of blindness in adults under age 65, and another, aging-related maculopathy, is the leading cause of new cases of blindness in people aged 65 and older. Every year, an additional 19,000 Americans become blind from retinal and choroidal disorders.

Intensive research over the last several years has led to dramatic improvements in the diagnosis and treatment of retinal and choroidal diseases, and in restoring vision lost from some of these conditions. However, the fact that many of the diseases in this group are still poorly understood indicates the need for a considerable amount of additional research in this field.

Subprograms. For the purpose of analysis, evaluation, and planning the National Eye Institute's Retinal and Choroidal Diseases program is divided into four categories, which consist of a total of 14 subprograms that reflect the major diseases and areas of basic research the program includes.

The following is a brief description of the major research areas encompassed by these subprograms. For a detailed assessment of their current status and future prospects see the complete *Report of the Retinal and Choroidal Diseases Panel* (Volume Two, Part One).

Vascular, Inflammatory, and Neoplastic Disorders of the Retina and Choroid

1. Diabetic Retinopathy, Sickle Cell Retinopathy, and Other Vascular Abnormalities

2. Inflammatory Disorders
3. Tumors

Degenerative Disorders of the Retina

4. Developmental and Hereditary Disorders
5. Macular Degeneration
6. Retinal Detachment and Vitreous Disorders
7. Toxic and Environmental Disorders

Fundamental Processes and Retinal Disorders

8. Retinal Pigment Epithelium
9. Photoreceptors, Visual Pigments, and Phototransduction
10. Retinal Organization, Neurotransmission, and Adaptation
11. Glial Cells and the Retinal Microenvironment
12. Rescue and Regeneration of Neurons in the Optic Nerve and Retina

Related Areas of Research Opportunity and Need

13. Noninvasive Techniques in the Study of Retinal Disorders
14. Tissue Acquisition and Distribution: Human Donor Eyes and Animal Models

Diabetic Retinopathy and Other Retinal Vascular Diseases. Diseases affecting the retinal blood vessels are among the major causes of visual disability and blindness in the United States. Although laser treatment has been proved to be highly effective in forestalling severe visual loss from diabetic retinopathy at certain stages of the disease and vision lost can in some instances be restored through a surgical procedure known as vitrectomy, improved therapies and means of prevention are still being sought. Other retinal vascular disorders affect more than 85,000 additional people each year and include retinopathy of prematurity (retrolental fibroplasia), which causes blindness in premature babies; sickle cell retinopathy; retinal vein occlusion; and hypertensive and atherosclerotic vascular disease.

Macular Disease. Degeneration of the macula, the small area of the retina responsible for sharp central vision, is a leading cause of blindness in the United States. Each year an additional 165,000 persons, mainly in the older age groups, develop macular disease, making it a major national public health problem. In May 1982, results reported from a nationwide clinical trial sponsored by the NEI provided the first conclusive evidence that laser treatment can be highly effective in preventing severe visual loss from the neovascular type of aging-related maculopathy, which is characterized by the formation of abnormal new blood vessels between the retina and choroid near the macula. An estimated 90 percent of legal blindness from aging-related maculopathy is due to the neovascular form which affects approximately 116,00 people in the United States. Evidence from this study suggests that as many as 89 percent of such cases of blindness could be prevented or delayed significantly by laser treatment. Although these results are impressive, much more research is needed to find better ways of treating and ultimately preventing aging-related maculopathy.

Retinitis Pigmentosa and Other Developmental and Hereditary Disorders. Developmental and hereditary disorders of the retina and choroid are responsible for 20 percent of all blindness due to chorioretinal diseases. Of these, retinitis pigmentosa, a progressive inherited disease, causes night blindness and a gradual restriction of the visual field and accounts for nearly 1,450 new cases of legal blindness each year. It has been estimated that between 50,000 and 100,000 people are afflicted with the disease in this county. Retinitis pigmentosa, like most of the disorders in this category, primarily strikes the young, causing them a lifetime of hardship, including heavy financial and emotional burdens.

Uveitis and Other Inflammatory Disorders. Inflammatory disorders of the retina and choroid comprise a large group of destructive, often painful, diseases, referred to as uveitis. These diseases often affect not only the retina and choroid but also the vitreous body, the transparent gel that fills the center of the eye, and the front of the uvea (the ciliary body and iris). Involvement of the anterior uveal tissues may result in secondary glaucoma and cataract. In 1978, approximately 45,000 new cases of uveitis were diagnosed in the United States.

Retinal Detachment. Retinal detachment and vitreous disorders that lead to a separation of the neural retina from the underlying pigment epithelium affect more than 25,000 people in the United States each year. Although research has made it possible to reattach the retina surgically in the majority of cases, approximately 8,300 people in the United States have suffered irreparable damage and extensive loss of vision from retinal detachment which could not be corrected. In addition, separation of the vitreous from its normal attachment sites is an important factor in diabetic retinopathy, which is related to the abnormal blood vessel growth and subsequent vitreous hemorrhage characteristic of this disease.

Tumors. Tumors of the retina and choroid, principally choroidal melanoma and retinoblastoma, have a relatively low incidence, but their importance is magnified by the fact that these forms of ocular cancer can cause death as well as blindness. About 1,500 new cases of choroidal melanoma are diagnosed annually in the United States, with an overall mortality rate after 5 years of 35 to 90 percent, depending on the size and malignancy of the tumor. Retinoblastoma is probably the most common of all congenital tumors affecting the newborn; it appears to occur more frequently among black children.

Although the tumor is responsive to various forms of treatment, the visual loss it causes is usually severe and permanent.

Toxic and Environmental Disorders. A concern that cuts across all retinal research is the effect of toxic or environmental agents which, acting separately or in concert, can severely damage the retina, even at levels apparently harmless to other tissues. In addition, drugs introduced into the eye or bloodstream may affect the retina and optic nerve adversely with serious consequences for visual function.

Critical Areas of Basic Research. Because the eventual prevention and improved diagnosis and treatment of retinal and choroidal diseases depends in large part upon better understanding of the normal and abnormal structure and function of the retina at the cellular and molecular levels, the following subprograms in which basic retinal research is conducted are critical.

Retinal Pigment Epithelium. The retinal pigment epithelium is a single cell layer that is vital to the health and survival of the rods and cones. Among the pigment epithelium's many functions are the selective transport of nutrients to and from the photoreceptors and the daily removal of discarded photoreceptor debris. Photoreceptor death and loss of visual function within the affected area can result if pigment epithelial cells are not functioning normally. In addition, the pigment epithelial cells may help keep the sensory retina in its proper position, a potentially significant factor in preventing retinal detachment.

Visual Cells. The photoreceptors are adversely affected by a wide variety of choroidal and retinal disorders. They are often the first cells to degenerate or suffer damage from hereditary defects (such as retinitis pigmentosa), retinal detachment, nutritional deficiencies, circulatory disturbances, and the toxic effects of drugs. Before the particular ways in which specific disease processes alter the metabolism and structure of the visual cells can be determined, it is essential that all aspects of their normal functioning be understood.

Retinal Organization. Knowledge of how the millions of complex retinal nerve cells are organized, the chemical substances that transmit information between nerve cells, and the molecular events that subserve visual phototransduction and adaptation (the reaction of the retina to light) is fundamental to the prevention, diagnosis, and treatment of retinal and choroidal diseases. It is also important to recognize that the retina is a part of the brain, and that insights into abnormalities in visual function will likely result in better understanding of a number of neurological brain disorders.

Program Goals

- To increase basic knowledge of the development, metabolism, molecular structure, and functional properties of the retinal neurons and the glial, choroidal, and pigment epithelial cells upon which they depend for maintenance and proper function.
- To develop procedures for the prevention and cure of diabetic retinopathy, retinal degeneration, retinal detachment, and other chorioretinal disorders, and conduct controlled clinical trials of promising new therapeutic measures as they become available.
- To devise noninvasive methods for probing the functional state of the human retina and its neighboring tissues, as an aid in diagnosis and in identifying the cellular elements involved in disease processes.
- To investigate in animals affected with retinal and choroidal diseases the genetic, biochemical, and immunological bases of the pathological processes, and the effectiveness of innovative therapeutic approaches.
- To identify nutritional and environmental factors that may be toxic to the retina, interfere with its normal development, or affect the long-term survival of the visual cells.
- To improve methods for maintaining retinal and choroidal cells in tissue culture, for investigating normal and pathological cellular mechanisms, analyzing the molecular basis of neurotransmission, testing the efficacy of new forms of therapy, and discovering the factors that promote neuronal growth and regeneration.
- To establish a sound basis for prognosis, genetic counseling, and medical intervention by determining the etiology, natural history, and epidemiology of inflammatory disorders, tumors, and the various degenerative diseases affecting the retina and choroid.

Current Support

The National Eye Institute is the major funding agency for research related to retinal and choroidal structure, function, and disease. In FY 1981, the NEI supported 381 research project grants in this field at a total cost of almost $34 million. Twenty-four contracts, amounting to almost $3.5 million, supported three multicenter clinical trials: the Diabetic Retinopathy Study, the Diabetic Retinopathy Vitrectomy Study, and Early Treatment Diabetic Retinopathy Study. Additional support in this field came from other NIH Institutes, other Federal

agencies, and several private foundations (see *Volume Three*).

Recent Accomplishments

- Demonstration through a collaborative clinical trial that argon laser photocoagulation can preserve vision in patients with the neovascular form of aging-related maculopathy, a finding that potentially could save an estimated 13,000 people a year from blindness.
- The initiation of two collaborative clinical trials to investigate further the use of vitrectomy surgery and early laser photocoagulation in diabetic retinopathy.
- The initiation of a collaborative clinical trial to investigate the value of argon laser photocoagulation in controlling the major complications of branch retinal vein occlusion.
- Development of a new primate model of abnormal retinal blood vessel growth that makes possible new approaches to studying macular degeneration.
- New ways of diagnosing retinal and choroidal disorders, including improvements in ophthalmoscopic techniques; ultrasound for locating intraocular foreign bodies, lesions, and tumors; and vitreous fluorophotometry for revealing early changes in retinal blood vessels, such as those preceding overt diabetic retinopathy.
- Major advances in the treatment of retinal hemorrhages, retinal detachments, diabetic retinopathy, some forms of uveitis, and other retinal disorders through further development and application of vitrectomy surgical techniques.
- Better understanding of the blood-retinal barrier in the normal retina and of the breakdown of the barrier in diabetic retinopathy and other vascular disease.
- Early diagnosis of retinitis pigmentosa and the use of electroretinography to detect carriers of the X-linked form of the disease.
- The identification of a specific enzyme defect in patients with gyrate atrophy, a rare retinal degenerative disease resembling retinitis pigmentosa, which may lead to a means of treatment.
- Advances in the identification and isolation of infectious agents that cause uveitis and a better understanding of the immunologic basis for certain inflammatory conditions of the retina and choroid.
- New drug and surgical approaches to the treatment of infectious ocular disorders.
- Better understanding of the genetics of retinoblastoma and of chromosomal changes associated with this form of ocular cancer, and the establishment of tumor cell lines for detailed laboratory investigations.
- The identification of specific metabolic defects in animals with hereditary retinal degeneration.
- The identification of retinal neurotransmitters, chemical messengers that make communication possible between cells in the retina.
- Better surgical management of retinal detachments and retinal breaks as a result of new instrumentation and other technical advances.
- Better understanding of the cellular properties of the retinal pigment epithelium, and the central role played by this single cell layer in the survival and function of the visual cells.
- Rapid progress in determining how the retina converts the light striking it into nerve impulses, how the retina begins processing visual information, and how this information is transmitted to the brain.
- The successful isolation of the messenger-RNA that codes for the visual pigment opsin, opening the possibility for direct genetic studies of visual pigment structure and genomic organization, and of possible defects in visual pigments associated with retinal degenerative disease.
- Advances in tissue and organ culture that make possible more detailed laboratory investigations of retinal blood vessel, nerve, and pigment epithelial cells.

Research Needs and Opportunities

- Clinical trial to determine whether rigorous blood sugar control in diabetes is effective in preventing retinal problems, including retinopathy.
- Basic studies of retinal vessel diseases including the use of tissue culture of capillary endothelial cells to identify factors that may cause the formation of abnormal new blood vessels in disorders such as diabetic retinopathy.
- The development of precise techniques for measuring retinal blood flow and oxygenation and for assessing the blood-retinal barrier.
- Investigation of ways to prolong retinal survival following blood vessel occlusions and to restore retinal function after such an occlusion.
- Identification of specific agents that cause uveitis and analysis of immunologic events and genetic factors involved in this disorder.

- Assessment of new drug and immunological approaches to the management and prevention of uveitis.
- Identification of risk factors, such as sex, age, environmental exposure, and race, that may be associated with the incidence of well-classified ocular tumors.
- Establishment of a human choroidal melanoma cell line and the development of animal models of choroidal melanoma for biochemical, immunologic, and chemotherapeutic studies.
- Investigation of the genetic factors involved in the development of retinoblastoma.
- Intensified search for functional, biochemical, and genetic defects in retinitis pigmentosa and other hereditary and developmental disorders of the retina and choroid.
- Clinical trials of the efficacy of photocoagulation in treating the subretinal neovascular membranes in macular degeneration and other disorders.
- Basic research into the genetic, antigenic, and environmental factors that cause abnormal blood vessels to develop beneath the retina, and the aging-related biochemical changes in Bruch's membrane (which separates the retina from the choroid) that enable the choroidal vessels to grow to the retina beneath the macular region.
- Investigation of drugs, for example, alpha-adrenergic blockers, for treating cystoid macular edema, a swelling of the central retina that causes markedly reduced vision.
- Basic research on the development, structure, and function of the normal vitreous, and on the mechanisms of abnormal cellular proliferation and membrane formation in the vitreous cavity.
- Research on the immunological role of the vitreous in the development of uveitis.
- Assessment of the potential toxicity to the retina of chemical and environmental agents, especially utilizing new, improved tissue culture techniques and epidemiological studies.
- Clarification on the role of the retinal pigment epithelium in producing adhesive forces that keep the retina in place or, when they fail, contribute to retinal detachment.
- Investigation of aging- and disease-related changes that occur within the photoreceptor cells and the retinal pigment epithelium which may affect normal cellular maintenance and function.
- Studies of the many roles of the retinal pigment epithelium in the normal eye and in inflammatory diseases, macular degeneration, and other retinal disorders.
- Research on photoreceptor metabolism and the mechanisms that regulate it, and on the role of aging, exposure to light, and nutritional deficiencies in the degeneration of these visual cells.
- Better understanding of the intricate "wiring system" linking retinal nerve cells, to define precisely the various pathways for information flow through the retina and the chemicals serving as messengers between cells.
- Definition of the role of the retinal microenvironment—the non-neuronal cellular elements and fluid within which the retina nerve tissue resides and functions—in retinal health and disease.
- Improved understanding of how the retina adapts to different levels of light and of the measurable electrical signals generated by the retina.
- Development of sensitive, easily applied, noninvasive procedures to test for specific retinal diseases.
- Exploration of how damaged retinal and optic nerves can be restored to normal functioning.
- Identification of factors which normally might promote the survival of retinal nerve cells and prevent the abnormal proliferation of glial elements, cells that provide structural support and perform important metabolic functions in the retina.
- Acquisition and distribution of human donor eyes for research as soon as possible after death as well as animal models with inbred or acquired ocular pathology.
- Development of new animal models of various retinal diseases and creation of adequate facilities to breed these animals for interested investigators.

Training and Manpower Needs

The realization of the above research goals and fulfillment of the foregoing needs will depend on the availability of a dedicated cadre of well-trained, innovative investigators. It is hoped that, spurred by this report and by the astonishing pace of technological advance, a reorientation of many established vision scientists toward new areas of opportunity will occur. But this will not be enough. To a significant extent, real progress will depend on the attraction to vision research of new investigators with special skills. Opportunities have been highlighted in the Plan for scientists trained in the basic research areas—neuroscience, molecular biology, pharmacology, physiology, biomedical engineering, optics, psychophysics, and immunology—to apply their talents and skills to problems in vision research. There is also a great need for the clinician

investigator who is uniquely trained to recognize opportunities for research on human diseases and to formulate, design, and carry out projects to capitalize upon them. Increasingly, clinically relevant questions can be asked at the cellular and molecular level; thus, the need for the interaction of well-trained basic science and clinician investigators and the pooling of their diverse talents is clear.

Special attention should be placed on training investigators in the following areas as they relate to research on the disorders of the retina and choroid:

- Genetics and molecular biology;
- Immunology;
- Nutrition and metabolism;
- Pharmacology and toxicology;
- Control of cellular proliferation;
- Epidemiology and biostatistics;
- Neuroscience (retinal development, regeneration, and plasticity); and
- Noninvasive tests of retinal function.

Highlights of Program Development Priorities

- Exploiting technological advances in the fields of molecular biology, cell physiology, and tissue culture in basic research on retinal cells and tissues.
- Assessing new drug and immunological approaches to the treatment and prevention of uveitis and other inflammatory disorders.
- Expanding biochemical and metabolic studies of Bruch's membrane (which separates the retina from the choroid), the adjacent retinal pigment epithelium, and the photoreceptors in the central retina, to provide new insights into aging-related maculopathy, other retinal degenerations, and retinal detachment.
- Intensifying the search for biochemical and genetic defects in retinitis pigmentosa and other hereditary retinal degenerative diseases, utilizing new molecular biology techniques.
- Characterizing neurotransmitters, the chemical substances that relay messages from one retinal nerve cell to another, with the aim of developing drug therapies for retinal neural disorders.
- Developing and applying better noninvasive tests of retinal physiology and of visual function in normal and pathological conditions.
- Performing studies of retinal capillary cells in tissue culture to elucidate the mechanisms of neovascularization, the abnormal growth of new retinal blood vessels, and the hemorrhaging that occurs in diabetic retinopathy, sickle cell retinopathy, and other vascular disorders.
- Conducting basic research on retinal detachment to determine what stimulates and controls the abnormal cellular proliferation and membrane formation in the vitreous humor that increases the damage in this condition.
- Assessing the damaging effects of environmental factors, nutritional deficiencies, and drugs on retinal function and developing screening systems for ocular toxicity.
- Pursuing new approaches to research on the basic biology, immunology, and genetics of sight- and life-threatening intraocular tumors.

Summary Resource Table

(Dollars in Thousands)

Subprograms	FY 1981 Grants* Cost		Panel Recommendation FY 83 Add. Grants Cost		Total Grants Cost**	
1. VASCULAR, INFLAMMATORY, AND NEOPLASTIC DISORDERS OF THE RETINA AND CHOROID						
a. Diabetic Retinopathy, Sickle Cell Retinopathy, and Other Vascular Abnormalities	51 $5,127	(13%)	9 $1,131	(8%)	60 $6,300	(12%)
b. Inflammatory Disorders	14 $1,558	(4%)	11 $1,067	(10%)	25 $2,625	(5%)
c. Tumors	18 $1,887	(5%)	11 $1,158	(10%)	29 $3,045	(6%)

* Includes R01, R10, R23, P50, K04, and K07 mechanisms.

** Estimated average cost of grants in Retinal and Choroidal Diseases program for FY 1983 is $105,000.

Subprograms	FY 1981 Grants*		Panel Recommendation FY 83 Add. Grants		Total Grants**	
	Cost		Cost		Cost	
2. DEGENERATIVE DISORDERS OF THE RETINA						
a. Developmental and Hereditary Disorders	42 $3,809	(11%)	17 $2,386	(15%)	59 $6,195	(12%)
b. Macular Degeneration	18 $1,418	(5%)	16 $2,152	(14%)	34 $3,570	(7%)
c. Retinal Detachment and Vitreous Disorders	18 $1,722	(5%)	9 $1,113	(8%)	27 $2,835	(5%)
d. Toxic and Environmental Disorders	2 $91	(1%)	2 $329	(2%)	4 $420	(1%)
3. FUNDAMENTAL PROCESSES AND RETINAL DISORDERS						
a. Retinal Pigment Epithelium	24 $1,931	(6%)	13 $1,954	(12%)	37 $3,885	(8%)
b. Photoreceptors, Visual Pigments, and Phototransduction	112 $9,514	(29%)	0 $2,246	(0%)	112 $11,760	(23%)
c. Retinal Organization, Neurotransmission, and Adaption	64 $4,729	(16%)	7 $2,726	(6%)	71 $7,455	(14%)
d. Glial Cells and the Retinal Microenvironment	6 $437	(1%)	3 $508	(3%)	9 $945	(2%)
e. Rescue and Regeneration of Neurons in the Optic Nerve and Retina	2 $136	(1%)	5 $599	(5%)	7 $735	(1%)
4. RELATED AREAS OF RESEARCH OPPORTUNITY AND NEED						
a. Noninvasive Techniques in the Study of Retinal Disorders	10 $1,176	(3%)	8 $714	(7%)	18 $1,890	(4%)
b. Tissue Acquisition and Distribution: Human Donor Eyes and Animal Models	[0] —		[6] —	***	[6] —	***
Total	**381** **$33,535**	**(100%)**	**111** **$18,083**	**(100%)**	**492** **$51,660**	**(100%)**

* Includes R01, R10, R23, P50, K04, and K07 mechanisms.

** Estimated average cost of grants in Retinal and Choroidal Diseases program for FY 1983 is $105,000.

*** Grants counted elsewhere within Retinal and Choroidal Diseases.

CORNEAL DISEASES

Introduction

The cornea is the transparent tissue at the front of the eye which plays a key role in refracting or bending light to focus images sharply on the retina. Because the cornea is the most exposed surface of the eye, it is particularly vulnerable to damage from injury, infection, toxic agents, and environmental pollutants. The normal cornea has no blood vessels and is nourished by the fluids that bathe it.

Corneal diseases and injuries account for only about 6 percent of all legal blindness in the United States, but are the primary cause of blindness worldwide. In addition, they are the most painful of all ocular disorders and account for considerable disability. In the United States approximately 62 percent of all annual cases of eye diseases affect the cornea. They account for more than 100,000 hospital days, $12 million in surgical costs, and more than 8 million office visits annually for professional eye care. Eye injuries, which primarily affect the cornea, account for an additional $1.7 million annual visits to physicians.

Subprograms. For purposes of analysis, evaluation, and planning, the National Eye Institute's Corneal Diseases program is divided into the following five subprograms which indicate the scope and diversity of current research in this field. These categories are in many ways interrelated so that advances in one may have a major influence on others.

1. External Ocular Infections and Inflammatory Diseases
2. Ocular Surface Problems
3. Refractive Problems and Contact Lenses
4. Corneal Edema, Endothelial Dysfunction, Dystrophies, and Inherited Diseases
5. Corneal Transplantation and Wound Healing

A detailed definition and description of each of these subprograms, many of which are further divided into research areas, can be found in *Volume Two, Part Two, Report of the Corneal Diseases Panel.* A brief discussion of each subprogram follows.

External Ocular Infections and Inflammatory Diseases. Herpes simplex virus is the leading infectious cause of corneal blindness and visual impairment in the United States. Acute ocular herpes infections are difficult to treat, even though a number of effective antiviral drugs are now available, because following the initial attack, the virus may become latent in nerve tissue behind the eye, only to reactivate periodically and cause the disease to recur. Up to 500,000 new cases of ocular herpes infections occur annually, of which approximately 50 percent recur. Medical therapy of ocular herpes requires frequent visits to physicians over periods ranging from several weeks to several months.

The eye is widely considered the best model for herpes research, and eye researchers have been among the leaders in this field, developing effective therapies for both ocular and systemic herpes infections. Eye researchers developed and tested the first effective antiviral drug, idoxuridine, and continue to play a major role in developing and testing other antiviral agents, including the newer recombinant DNA-produced interferons. Another important accomplishment has been the discovery of where the latent herpes virus resides between acute ocular infections. The finding of latent herpes virus in the trigeminal ganglion, a bundle of central nerve cells that innervate the nerve cells of the eye, face, and head, has implications for research on recurrent herpes infections elsewhere in the body as well. Because most ocular infections, whether from viruses, bacteria, fungi, or other agents, can lead to severe visual complications and can spread to other body organs, a large portion of the NEI Corneal Diseases program is devoted to the study of herpes simplex and other ocular infections and the immune mechanisms involved in the body's response to them.

Ocular Surface Problems. The tear film on the cornea's surface helps protect it from injury, infection, and the environment and also serves as the major element in light refraction. Changes in the ocular surface can occur with aging, and dry eyes often result when the lacrimal glands fail to produce adequate amounts of tears to bathe the front of the eye. This can lead to serious irritation and eventual scarring of the cornea and can make the eye more vulnerable to injury and infection as the surface's protective effects are diminished. The surface of the cornea is particularly prone to foreign body injuries and superficial ocular infections which are responsible for many visits to ophthalmologists' offices and hospital emergency rooms. Furthermore, many surface defects, such as those caused by chemical burns, heal very slowly.

Refractive Problems and Contact Lenses. Nearly 100 million people in the United States have refractive errors—nearsightedness, farsightedness, or astigmatism—that require correction, usually by glasses or contact lenses. Contact lenses are also used by many people following cataract surgery, by children with amblyopia and other sensorimotor defects, and as a component of some of the sight-enhancing aids for patients with low vision problems.

Over the last 25 years, techniques have been introduced for correcting refractive errors surgically by changing the curvature of the cornea. This field is expected to develop rapidly over the next

few years. One of the most widely publicized of these operations is radial keratotomy, in which a series of linear incisions is made on the corneal surface in a pattern similar to spokes on a wheel. These cuts weaken the corneal tissue so that internal eye pressure makes the edge of the cornea bulge slightly, flattening the central part and thereby improving the focus of the visual image onto the retina. Other surgical methods to change refraction include grafting, as in epikeratophakia in which specially shaped donor corneal tissue is grafted onto the front of the patient's eye, and keratomileusis in which a thin section of corneal tissue is removed from the patient's own eye, precisely reshaped to a form that will improve the eye's focusing ability, and then replaced. The long-term safety and efficacy of these procedures are still under investigation. Important advances have also been made in the nonsurgical treatment of refractive errors, particularly in the development of gas permeable and extended-wear contact lenses, constructed from new biopolymers.

Corneal Edema, Endothelial Dysfunction, Dystrophies, and Inherited Disease. This subprogram encompasses basic research on normal and abnormal corneal development, structure, and function. Investigation of normal corneal structure includes studies of how the cornea is nourished and kept transparent. The cornea is divided into three cellular layers, each of which plays a role in keeping it transparent: the outer multicellular epithelial layer, the middle stromal layer, and the inner endothelial single cell layer. The stroma must be maintained at a specific level of hydration if it is to remain transparent. The NEI funds research aimed at understanding normal stromal function and hydration and the changes in this layer that occur in disease. Herpes infections, for example, frequently produce irreversible structural changes in the stroma which result in corneal scarring that may lead to blindness.

Increased knowledge of the mechanisms which control the turnover of the large molecules that make up the cornea will help in understanding and improving corneal wound healing and improve the ability to culture and transplant corneal cells and tissues. Although the incidence of corneal dystrophies and inherited disorders is not very high, they do cause severe visual disability, discomfort, and inconvenience to affected patients, and require long-term medical care.

Corneal Transplantation and Wound Healing. Many people who a generation ago would have been permanently blinded by corneal injury or infection, inherited corneal disease, or corneal degeneration can now often have their sight restored through corneal transplantation, an operation performed on approximately 15,000 eyes annually in the U.S. alone. This is one of the oldest and most successful tissue transplant procedures, dating from the 1940s and continuously improved since that time. However, it is only during the last decade that complication rates in corneal transplantation have been greatly reduced due to increased knowledge of normal corneal development and function, improved understanding of the basic immunological processes underlying graft rejection, development of better operative techniques, use of finer sutures, and the development of better methods of tissue handling and preservation. The success rate for corneal transplantation in such noninflammatory conditions as keratoconus and corneal edema is now 80 to 95 percent.

Some important new instruments and techniques hold great promise for the future of corneal diseases research. One of these, the specular microscope, permits evaluation in the intact eye of the corneal endothelium. Specular microscopy is also used to evaluate the effect of intraocular surgical techniques on the endothelium. Such studies are important because this cell layer is vital in maintaining corneal clarity and in humans it does not readily regenerate following damage.

If the endothelium is damaged, transplantation of the whole cornea is now required. However, a promising new experimental technique has been developed that involves growing in tissue culture endothelial cells that line the inner walls of blood vessels. Because these cells appear to be quite similar to those of the corneal endothelium, they have been transplanted in eyes that might normally require a whole cornea to be grafted. In theory, this technique would make it feasible to remove a small piece of vein from the leg of patients requiring a corneal transplant, grow the endothelial cells from the vein in tissue culture, and then, two to three weeks later, transplant these cells from the patient's own vein onto the back of his or her cornea. Because the donor and the recipient can be the same individual, this strategy would eliminate the problem of tissue rejection. To date this technique has been performed only in animals, and many questions remain to be answered before it can be applied to humans.

Program Goals

- To improve means of preventing and treating ocular infections, particularly recurrent herpes virus infection.
- To develop more effective antiviral drugs and new techniques for drug delivery and determine drug effects on the ocular surface.
- To define the effects of corneal inflammation and develop methods for its control.

- To understand the composition of the normal tear film in relation to the ocular surface and changes that occur in disease and aging, including immunological mechanisms.
- To understand healing and regeneration of the ocular surface epithelium in relation to its underlying basement membrane.
- To develop better methods of evaluating, diagnosing, and treating patients with dry eye and tear film abnormalities.
- To develop and test new procedures for modifying corneal refraction.
- To understand the swelling properties of the corneal stroma and the factors governing corneal transparency.
- To understand normal corneal cell growth, metabolism, replacement, and repair and the pathogenesis of corneal developmental anomalies, dystrophies, and other inherited abnormalities, and find more effective means of treating these conditions.
- To determine the biological and biochemical bases of tissue destruction and scarring in the cornea and sclera.
- To improve the success rate of corneal transplantation and develop alternatives to whole cornea grafts from donor eyes.

Current Support

The NEI is the major source of support for research related to corneal structure, function, and disease. In FY 1981, the Institute funded 162 research grants at a total cost of almost $16 million in the Corneal Diseases program. Additional support in this field came from other NIH institutes, other Federal agencies, philanthropic organizations, and private industry, particularly those manufacturers of contact lenses who have supported research conferences and research projects related to the development and testing of their products.

Recent Accomplishments

- Successful treatment of ocular herpes simplex virus infection with several new antiviral agents, including idoxuridine, vidarabine, trifluorothymidine, and acycloguanosine (acyclovir).
- Better understanding of the disease process in ocular herpes virus infections, including the identification of latent viral reservoirs in neuronal tissue from which the active disease recurs and the nature of the immune response to infection.
- Development of the first ophthalmic antifungal agents and the beginning of clinical trial testing of these agents.
- Improved knowledge of the chemical basis for maintaining a healthy and stable tear film.
- Better understanding of corneal wound healing and the role of corneal vascularization.
- Development of conjunctival transplantation to resurface the damaged cornea.
- Improvements in contact lenses, largely by manufacturers, including the development and testing of extended-wear lenses and new gas-permeable hard lens materials, for those whose refractive error is not corrected by flexible lenses.
- Development of a variety of surgical procedures to correct refractive error by changing the cornea's shape.
- Ability to grow corneal endothelium in tissue culture and successfully transplant it in animals.
- Recognition that intraocular surgery can damage the corneal endothelium, which has led to the development of improved surgical techniques and a decrease in endothelial damage and blindness caused by corneal edema.
- Discovery of how fluid is actively transported in the corneal endothelium and subsequent development of a working mathematical model for control of corneal hydration.
- Improved characterization and understanding of several corneal dystrophies.
- Improved selection and handling of donor eyes combined with improved preservation and surgical techniques resulting in an overall higher success rate for corneal transplantation.
- Use of the specular microscope to screen corneal donor material for transplantation and thereby select the best quality tissue to transplant.
- Use of modified antibodies to block transplant rejection in an animal model.

Research Needs and Opportunities

- Additional studies of how corneal cells become infected and of the immunologic aspects of various forms of ocular viral, bacterial, and fungal infections in animal models and humans, that are aimed at improved treatment, including immunotherapy.
- Further evaluation of ocular herpes simplex virus latency and recurrence, including the neural, viral, and host factors responsible.

- Additional studies of fluid secretion by the lacrimal gland, of the tear film in normal and diseased eyes, and of the relationship of the tear film to the eyelid and underlying ocular surface for the purpose of developing new therapies for tear abnormalities.
- Development of an animal model for recurrent corneal erosion and persistent defects.
- Study of the immunology of the ocular surface.
- Finding the causes of abnormalities in the diabetic corneal epithelium.
- Development of alternative methods for continuous drug delivery and tear substitutes and assessments of their effects on corneal epithelial cells.
- Studies of the normal cornea, using better methods for measuring its optical and physiological properties, and determining the factors that allow its shape to be manipulated.
- Development and evaluation of new tests, procedures, and materials to improve visual acuity by modifying corneal refractive properties, including surgical and lens corrections.
- Functional evaluation of tissue culture of all cell layers of the cornea and comparison of the normal, degenerative, and dystrophic corneal endothelium.
- Further development of techniques for transplantation of tissue-cultured corneal endothelium.
- Further evaluation of instruments used in corneal research, such as pachymeters for measuring corneal thickness, fluorometers to study tear flow and tear secretion, and the specular microscope to evaluate the functional effects of therapeutic measures on the corneal endothelium.
- Comparison of fluid transport in the normal endothelium with that of cultured endothelial cells.
- Elucidation of changes in corneal stromal properties caused by corneal dystrophies, other diseases, and aging.
- Continuing investigation of the physical basis for corneal transparency and its alteration in specific disease processes.
- Investigation of new agents such as progestational steroids in preventing both inflammation and formation of ulcers and in promoting wound healing.
- Increased understanding of corneal transplant immunology and its role in corneal graft rejection.
- Further study of endothelial cell transplantation as an alternative to whole corneal transplantation.

Training and Manpower Needs

- Fellowships in immunology, microbiology, virology, biochemistry, cell biology, and pharmacology for ophthalmologists who have completed their residency training and have little or no previous research experience. The need for fellows is greatest in epidemiological research on corneal disease risk factors and clinical research directed at the treatment of external diseases of the eye.
- Short-term training for both basic and clinical scientists with prior experience in connective tissue research to explore basic biochemical, immunologic, and/or physiologic mechanisms that center on the interrelationships among the various cell layers of the cornea and between these layers and adnexal glands.
- To promote interest in refractive problems and their correction, postdoctoral fellowships and pilot project grants are recommended.

Highlights of Program Development Priorities

- Determining the neuronal and viral factors contributing to the latent period of herpes infection.
- Continuing development of antiviral drugs for treatment of acute and recurrent corneal infections.
- Continuing development of methods to stimulate repair of the diseased or injured corneal endothelium, especially in primates, and improving corneal transplant procedures using cultured endothelial cells as a possible replacement for donor tissue.
- Studying the biological effects of existing and proposed surgical procedures and optical devices for correcting refractive error.
- Evaluating immunological mechanisms of the ocular surface and their role in health and disease.
- Studying the frequently painful abnormalities of the ocular surface, their causes and persistence, and establishing their relationship to the cornea's neural supply.
- Investigating the changes that occur with disease and aging in the biochemistry of the corneal stroma.
- Improving understanding of the biochemistry and immunological components of the cornea's response to injury and wound healing, determining the importance of specific immunological factors in corneal transplantation, and developing and testing drugs which can modify or eliminate immune reactions to transplanted tissue.

Summary Resource Table

(Dollars in Thousands)

Subprograms/Areas	FY 1981 Grants* Cost		Panel Recommendation FY 1983 Add. Grants Cost		Total Grants Cost**	
1. EXTERNAL OCULAR INFECTIONS AND INFLAMMATORY DISEASE						
a. Herpes Simplex	21 $2,153	(13%)	7 $843	(13%)	28 $2,996	(13%)
b. Herpes Zoster	0 0	(0%)	2 $214	(4%)	2 $214	(1%)
c. Adenovirus and Enterovirus	1 $130	(1%)	2 $191	(4%)	3 $321	(1%)
d. Bacterial and Fungal Keratitis	9 $702	(6%)	3 $582	(6%)	12 $1,284	(6%)
e. Chlamydial Keratoconjunctivitis	7 $879	(4%)	1 -$23	(1%)	8 $856	(4%)
f. Chronic Blepharitis	2 $167	(1%)	2 $261	(4%)	4 $428	(2%)
g. Other Infections	2 $289	(1%)	0 -$75	(0%)	2 $214	(1%)
Subtotal	**42** **$4,320**	**(26%)**	**17** **$1,993**	**(32%)**	**59** **$6,313**	**(28%)**
2. OCULAR SURFACE PROBLEMS						
a. Tear Film and Its Abnormalities	10 $750	(6%)	1 $427	(2%)	11 $1,177	(5%)
b. Ocular Surface Disorders	30 $3,021	(18%)	5 $724	(9%)	35 $3,745	(16%)
c. Drug Delivery and Toxicity	1 $126	(1%)	1 $88	(2%)	2 $214	(1%)
Subtotal	**41** **$3,897**	**(25%)**	**7** **$1,239**	**(13%)**	**48** **$5,136**	**(22%)**
3. REFRACTIVE PROBLEMS AND CONTACT LENSES	19 $1,682	(12%)	7 $1,100	(13%)	26 $2,782	(12%)

* Includes R01, R10, R23, P50, K04, and K07 mechanisms.

** Estimated average cost of grants in Corneal Diseases program for FY 1983 is $107,000.

Subprograms/Areas	FY 1981 Grants* Cost		NAEC Recommendation FY 1983 Add. Grants Cost		Total Grants Cost**	
4. CORNEAL EDEMA, ENDOTHELIAL DYSFUNCTION, DYSTROPHIES, AND INHERITED DISEASE						
a. Endothelial Tissue Culture, Replacement, and Repair	5 $585	(3%)	2 $164	(4%)	7 $749	(3%)
b. In Vivo Evaluation of Corneal Epithelial and Endothelial Membrane Function	3 $259	(2%)	2 $276	(4%)	5 $535	(2%)
c. In Vivo Morphologic Evaluation--Specular Microscopy	2 $238	(1%)	1 $83	(2%)	3 $321	(1%)
d. Endothelial and Epithelial Transport Processes (Corneal Hydration and Edema)	10 $1,196	(6%)	3 $195	(6%)	13 $1,391	(7%)
e. Stromal Swelling and Transparency	7 $570	(4%)	1 $286	(1%)	8 $856	(4%)
f. Normal Corneal Development	2 $181	(1%)	0 $33	(0%)	2 $214	(1%)
g. Corneal Dystrophies, Inherited Disorders, and Developmental Anomalies	4 $485	(3%)	3 $264	(6%)	7 $749	(3%)
Subtotal	**33** **$3,514**	**(20%)**	**12** **$1,301**	**(23%)**	**45** **$4,815**	**(21%)**
5. CORNEAL TRANSPLANTATION AND STROMAL WOUND HEALING						
a. Inflammation and Repair	16 $1,256	(10%)	4 $884	(8%)	20 $2,140	(9%)
b. Corneal Transplantation	11 $1,180	(7%)	6 $639	(11%)	17 $1,819	(8%)
Subtotal	**27** **$2,436**	**(17%)**	**10** **$1,523**	**(19%)**	**37** **$3,959**	**(17%)**
TOTAL	**162** **$15,849**	**(100%)**	**53** **$7,156**	**(100%)**	**215** **$23,005**	**(100%)**

* Includes R01, R10, R23, P50, K04, and K07 mechanisms.

** Estimated average cost of grants in Corneal Diseases program for FY 1983 is $107,000.

CATARACT

Introduction

A cataract is an opacity of the eye's normally clear lens that interferes with vision and is one of the most common and widely feared eye diseases. Although regarded by many people as an unavoidable and even inevitable accompaniment to advancing age, cataract may develop at any time in life, even before birth. In addition to aging, cataract may be a consequence of diabetes and other metabolic disorders, trauma, toxic environmental agents as radiation and light, or it may be inherited or congenital in nature.

About 60 percent of people between the ages of 65 and 74 show some signs of cataract, and about 3.3 million people in the United States are visually impaired by this disorder. At least 43,000 people are blind from cataract, making it the third leading cause of legal blindness in the United States; about 4,700 new cases of blindness resulting from cataract occur each year.

At present, surgery to remove the opaque lens is the only effective way of treating cataract. Techniques developed over the past 25 years have made cataract extraction one of the safest and most successful of all major operations. About 90 to 95 percent of the 540,000 cataract extractions performed each year in the United States at a total cost of $1.35 billion are successful in restoring useful vision when eyeglasses, contact lenses, or artificial lens implants are used. Nonetheless, because it is always desirable to avoid surgery if possible and because complications or unsatisfactory visual adjustments still occur following cataract extraction in a small percentage of cases, the National Eye Institute devotes most of its funding in the Cataract program to research aimed at developing means of preventing or slowing the development of cataracts or of treating them nonsurgically. It has been estimated that if it were possible to slow the progression of cataract enough to delay the need for surgery by only ten years, the number of cataract operations performed in the United States could be reduced by 45 percent annually, resulting in a savings of over $607 million dollars per year.

Subprograms. To focus attention on several distinct but interrelated aspects of cataract research, the NEI Cataract program has been divided into the following subprograms. This structure also provides a basis for Cataract program analysis, evaluation, and planning and for the organization of the Cataract Panel's report (Volume Two, Part Three).

1. The Normal Lens
2. Epidemiology of Cataract
3. Senile Cataract
4. Diabetic and Metabolic Cataract
5. Nongenetic Congenital and Genetic Cataracts and Dislocated Lenses
6. Cataract Induced by Environmental and Toxic Effects
7. Treatment of Cataract and Correction of Aphakia

Program Goals

- To find means of preventing or slowing cataract development.
- To determine the causes and mechanisms of cataract formation.
- To understand the development, biochemistry, and biophysics of the normal lens.
- To evaluate the safety and efficacy of methods of cataract extraction.
- To evaluate new methods for correcting optical problems that follow cataract surgery.

Current Support

Support for cataract research in the United States is provided mainly by the National Eye Institute. In FY 1981, NEI supported 101 individual cataract research grants at a total cost of nearly $9 million. This includes support for the Cooperative Cataract Research Group (see below). Other branches of the Federal Government provided limited support for cataract research. Private organizations contribute in many important ways to projects not funded by the NEI.

Recent Accomplishments

- Formation of a nationwide Cooperative Cataract Research Group, consisting of 22 research laboratories throughout the United States, that has helped focus and stimulate research on human cataract.
- Development of a standardized photographic system for classifying extracted human cataracts for laboratory study, which has resulted in, among other things, new findings concerning cataracts in different populations.
- Evidence that cataracts may result from oxidation of lens proteins, causing them to clump together and scatter light, thereby impairing vision.
- New knowledge of the embryology, growth, and development of the normal lens, including the role of hormones and growth factors involved in cell differentiation and division.

- Cloning of lens crystallin DNAs in bacteria to permit study of genetic control of lens cell activities.
- Improved understanding of normal lens metabolism.
- Epidemiologic confirmation of the increased risk of cataract in diabetics under age 65.
- Evidence supporting the hypothesis that sunlight exposure may be related to cataract development.
- Development of several potent chemical inhibitors of the enzyme aldose reductase, which triggers cataract formation in diabetic laboratory animals.
- Increasing evidence of the role of aldose reductase in causing human diabetic complications, notably diabetic retinopathy, which suggests a possible therapeutic use of aldose reductase inhibitors.
- Study of several animal models of genetic cataract, making it possible to investigate the genetic abnormalities underlying these opacities at the cellular and molecular level.
- Tissue culture of normal and cataractous animal lens cells, paving the way for human lens cell culture which could lead to determining the key genetic defect in human congenital cataracts.
- Use of x-ray-induced cataract in animals as a model for studying human senile cataract and DNA repair mechanisms in the lens.

Research Needs and Opportunities

- Additional studies of the basis for cataract formation with human aging.
- Studies of lens morphology, cell division, and protein synthesis.
- Further studies of the lens and lens epithelial cells in culture.
- Increased application of the techniques of molecular biology, including recombinant DNA technology, to the problems of cataract development.
- Further development of an objective, reproducible, and standardized classification of type and severity of cataract.
- Obtaining valid and reliable epidemiologic data on cataract occurrence, including determining the role of various environmental and genetic factors in cataract etiology; further study of the role of sunlight, ultraviolet light, other forms of ionizing and nonionizing radiation, and toxic chemicals in cataract development; further study of the association between cataract and diabetes, blood pressure, family history, nutrition, blood chemistry, and other possible risk factors; and studies of the natural history of senile cataract and associated risk factors.
- Further characterization of light-scattering molecules in senile cataract.
- Further study of the molecular structure of the plasma membrane of lens cells where the cataractous process may be initiated, and its interaction with other cellular elements.
- Further study of aldose reductase activity in normal and diabetic human lenses to determine whether this enzyme is involved in the refractive changes and fluctuations commonly experienced by diabetics.
- Investigation of the toxicology of aldose reductase inhibitors at therapeutic doses.
- Investigation of the genetics and natural history of inherited cataracts, including long-term, controlled familial studies.
- More complete biochemical characterization of the human lens zonules, the ligaments that support the lens and cause it to change its shape and focal strength when attention is directed to either near or far objects.
- Development of animal models of lens dislocation.
- Scientific comparison of various approaches to cataract surgery.
- Toxicologic studies of intraocular lenses.
- Studies of the mechanism of inflammation induced by intraocular lenses with the aim of developing improved devices.
- Evaluation of proposed medical (nonsurgical) methods of cataract treatment.

Training and Manpower Needs

New investigators should be recruited to cataract research, particularly epidemiologists, biostatisticians, molecular biologists, biochemists, medicinal chemists, and physicians with an interest in cataract/lens research. More clinicians, with special knowledge of the problems of cataract and its management are especially needed. The Cooperative Cataract Research Group might serve as a coordinating instructional resource, perhaps under the NEI institutional fellowship mechanism, for recruiting and training cataract researchers.

Highlights of Program Development Priorities

- Determining through epidemiologic studies factors that increase the risk of developing cataract.

- Studying the molecular biology of the normal lens and cataract, with emphasis on gene analysis and the structure and metabolism of nucleic acids.
- Developing an objective system for classifying cataracts in the living eye as a standard for research on cataract prevention and treatment.
- Studying the biochemical and biophysical properties of lens crystallins, particularly with regard to transparency, and the structure and function of the cytoskeleton, those protein elements that help the lens maintain its shape.
- Studying the potentially cataract-inducing effects of low doses of ionizing and microwave radiation, and the effects of environmental ultraviolet radiation on the lens.
- Comparing the results of various methods of cataract surgery and employing controlled clinical trials to determine the safety and efficacy of various methods of optical correction following cataract surgery, including intraocular lenses, contact lenses, and surgical modification of corneal curvature.
- Conducting further studies of the characteristics of the enzyme aldose reductase and developing safer and more effective aldose reductase inhibitors to delay diabetic cataract formation.

Summary Resource Table

(Dollars in Thousands)

Subprograms	FY 1981 Grants*	Cost	Panel Recommendation FY 1983 Add. Grants	Cost	Total Grants	Cost**
1. The Normal Lens	31	(30%)	7	(20%)	38	(28%)
	$3,145		$959		$4,104	
2. Epidemiology of Cararact	0	(0%)	7	(20%)	7	(5%)
	0		$756		$756	
3. Senile Cataract	24	(24%)	9	(25%)	33	(24%)
	$2,158		$1,406		$3,564	
4. Diabetic and Metabolic Cataract	19	(19%)	4	(11%)	23	(17%)
	$1,417		$1,067		$2,484	
5. Nongenetic Congenital and Genetic Cataracts and Dislocated Lenses	6	(6%)	5	(13%)	11	(8%)
	$530		$658		$1,188	
6. Cataract Induced by Environmental and Toxic Effects	11	(11%)	0	(0%)	11	(8%)
	$986		$202		$1,188	
7. Treatment of Cataract and Correction of Aphakia	10	(10%)	4	(11%)	14	(10%)
	$734		$778		$1,512	
Total	**101**	**(100%)**	**36**	**(100%)**	**137**	**(100%)**
	$8,970		**$5,826**		**$14,796**	

* Includes R01, R10, R23, P50, K04, and K07 mechanisms.

** Estimated average cost of grants in Cataract program for FY 1983 is $108,000.

GLAUCOMA

Introduction

There are many types of glaucoma, most of which are characterized by an abnormally high level of the fluid pressure within the eye (intraocular pressure), accompanied by progressive destruction of peripheral vision due to irreversible damage to the optic nerve.

Although glaucoma may occur at any time in life, and there are severe congenital forms of the disease, the risk of developing glaucoma increases with age. About 62,000 Americans are legally blind from glaucoma and about 1.2 million Americans are known to have this disease. In addition, as many as 10 million people may have elevated intraocular pressure, called "ocular hypertension," but show no optic nerve damage, although some eventually will develop glaucoma. Conversely, a significant number of people sustain optic nerve damage even though they have what is considered normal intraocular pressure. This condition is referred to as "low tension" glaucoma. At present, there is no sure way to predict which people, with or without ocular hypertension, are at risk for developing glaucoma or losing vision.

Normal intraocular pressure is maintained by balancing the continuous production of fluid within the eye and the rate of its drainage from the eye. This fluid, the aqueous humor, is produced primarily by the ciliary body, passes between the iris and the lens and fills the *anterior chamber*, the space between the lens and cornea, thereby providing nourishment to these transparent tissues which have no blood supply. Fluid leaves the eye by filtering through the trabecular meshwork and the *canal of Schlemm*, the tissues located in the area enclosed by the *angle* at the juncture of the iris and the cornea. Almost always it is the blockage of the aqueous humor exit pathways, rather than overproduction of fluid, that is the cause for the increased intraocular pressure in glaucoma.

Glaucoma is diagnosed by measuring intraocular pressure, observing typical changes in appearance of the *optic nerve head* with an ophthalmoscope, and measuring changes in the field of vision. Because the progress of glaucoma often can be stopped or slowed by drugs or surgery to reduce intraocular pressure, blindness may usually be prevented if the condition is detected and treated early. However, once vision is damaged or lost because of glaucoma, it cannot be restored.

Although glaucoma may be controlled, most forms of the disease cannot be cured. The predominant form of glaucoma, accounting for up to 80 percent of all cases of the disease, is known as primary open-angle glaucoma. In this condition and in ocular hypertension and low tension glaucoma, outflow of aqueous humor is impaired although no anatomic blockage is apparent in the filtration angle. Current research is focused on possible mechanisms involving submicroscopic particles which may clog the filtration channels.

Angle-closure glaucoma, which accounts for 10 to 20 percent of all glaucoma cases, is characterized by a narrower than normal filtration angle, caused by the iris and lens being closer to the front of the eye than they are in unaffected people. Intraocular pressure rises when aqueous humor outflow is impeded by the iris being pushed closer to the cornea, thus closing off the angle. In some patients, this can be controlled by drugs. In other cases, cutting a tiny hole in the iris can cure the disorder.

The fact that glaucoma remains a major cause of blindness, despite the availability of various ways of controlling intraocular pressure, indicates the need to understand better the mechanisms by which intraocular pressure causes optic nerve damage and to develop more effective means of early detection, prevention, and treatment.

Treatment for glaucoma, whether by drugs or surgery, is aimed at either diminishing aqueous humor production or facilitating its outflow. In the search for a cure for glaucoma, an understanding of the normal cellular processes that regulate the flow of aqueous humor through the eye, how they are changed as the disease is initiated and progresses, and how drugs act upon them is essential, as is determining how optic nerve damage is related to intraocular pressure. An understanding of the basic physiologic processes in the optic nerve which are affected in glaucoma ultimately should lead to the development of ways to protect the optic nerve and perhaps eventually to reverse nerve damage.

Subprograms. The National Advisory Eye Council's Glaucoma Panel has organized its recommendations for glaucoma research under the following subprograms to focus attention on major areas of emphasis and to facilitate program planning, analysis, and evaluation. Detailed consideration of each of these subprograms is given in the Panel's full report (Volume Two, Part Four).

Primary Open-Angle Glaucoma

1. Etiology, Epidemiology, Management, and Therapy
2. Aqueous Humor Dynamics: Inflow
3. Aqueous Humor Dynamics: Outflow
4. The Optic Nerve

Other Glaucomas

5. Angle-Closure Glaucoma
6. Developmental, Congenital, and Infantile Glaucomas
7. Secondary Glaucomas

The following is a brief discussion of the major types of glaucoma that the program addresses:

Primary Open-Angle Glaucoma and Angle-Closure Glaucoma. Primary open-angle glaucoma differs from the other types of glaucoma in that there is no anatomic evidence for blockage of the filtering area of the angle of the eye. Although in most patients open-angle glaucoma can be controlled by medications, for some people drug therapy is difficult, in others the disease is intractable. By contrast, in angle-closure glaucoma, the passage of aqueous humor into the front part of the eye and to the filtration tissues is physically impeded due to anatomic abnormalities. Recent improvements in surgical techniques and the development of effective laser treatments that create an opening in the iris to allow fluid to reach the filtration angle offer new hope for such cases.

Developmental, Congenital, and Infantile Glaucomas. Developmental, congenital, and infantile glaucomas are as yet a poorly defined group of diseases which are often hard to treat. They are due to maldevelopment of the eye in the area of the filtration tissues. Their relative rarity has made it particularly difficult to standardize methods of diagnosis, classification, and treatment. Research into these diseases is particularly needed, for failure to alleviate them may lead to lifelong blindness of the affected children.

Secondary Glaucomas. Secondary glaucomas develop as a consequence of other eye diseases or of trauma. Neovascular glaucoma, which is a very serious disease and can lead to loss of the eye, is caused by abnormal new blood vessels growing over the iris and occluding the filtration area; it often follows new vessel growth in the retina caused by diabetes. Other serious types of glaucoma result from ocular inflammation (uveitis), from contusions, following intraocular hemorrhage, or from a variety of ocular abnormalities.

It is essential to stimulate research on the fundamental causes of all types of glaucoma and on devising improved means for treating them.

Program Goals

- To prevent loss of vision in all types of glaucoma by improved means of detection, diagnosis, and therapy.
- To understand the basis of optic nerve damage in glaucoma and the reasons why the susceptibility to a given level of intraocular pressure varies in individual optic nerves.
- To describe the basic pathophysiology of the different types of glaucoma at the levels of cell, tissue, and organ, and how they may be altered therapeutically.
- To define the basic processes in the normal eye which regulate aqueous humor dynamics, and to determine how drugs used or proposed for use in therapy interact with them.
- To develop predictive measures for the onset and development of glaucoma, and particularly the detection of very early optic nerve damage, with special emphasis on noninvasive techniques.
- To conduct epidemiologic studies of the different types of glaucoma, including both natural histories and responses to treatment.

Current Support

In FY 1981, the NEI supported 90 glaucoma research grants at a total cost of about $9 million. A small amount of glaucoma research is supported by other Federal agencies. Modest grants from nongovernmental groups have aided several investigators in initiating their studies.

Recent Accomplishments

- Establishment of cells of the trabecular meshwork (the tissue through which aqueous humor filters before draining from the eye) in tissue culture and initiation of studies of their properties, which may lead to an understanding of the increased resistance to outflow of fluid from the eye.
- Electron microscopic studies of trabecular meshwork specimens from patients with primary open-angle glaucoma and steroid-induced glaucoma showing accumulations of specific extracellular materials which may obstruct aqueous humor outflow.
- Demonstration that the number of cells of the trabecular meshwork in normal eyes decreases with age, and that in eyes with primary open-angle glaucoma, matched for age, the number of cells per unit area of meshwork is reduced. This finding may be significant in defining the etiology or natural history of glaucoma.
- Introduction of new drugs for glaucoma therapy: timolol, which is relatively free of side effects, and dipivalyl epinephrine, which is more effective and has fewer side effects than epinephrine, and determining the basis of their action.
- Demonstrations that in man elevation of intraocular pressure induced by steroids (like hydrocortisone) is due directly to hypersensitivity of ocular tissues and is not a general cellular response, and characterization in rabbits of steroid-specific receptors (specific binding sites for steroids in cells) in trabecular and ciliary body-iris cells.

- Preliminary results showing that argon laser treatment can lower intraocular pressure in open-angle glaucoma.
- Treatment of angle-closure glaucoma by making a hole in the iris with a laser, an alternative to conventional iridectomy. Another laser technique involves shrinking the peripheral iris to keep the outflow angle open.
- Development of a plastic filtering valve, which allows aqueous humor to escape when intraocular pressure rises, for relief of eyes with intractable neovascular glaucoma.
- Development of a new microelectronic device, fitted into an eyedrop dispenser, which records the time of each use of medication for a month, to aid studies of how well patients comply with prescribed regimens.
- Demonstration in monkeys of a mechanism by which elevated intraocular pressure can damage the optic nerve. (Optic nerve axonal transport, the flow of essential substances in the optic nerve, was diminished, both by an acute rise in intraocular pressure and when high pressure was maintained over a long period, as in glaucoma.)
- Studies using fluorescein (an injected dye) have shown that in glaucoma some areas of the optic nerve have fewer blood vessels than normal, either the direct result of increased intraocular pressure obstructing their blood supply or of a secondary vessel loss accompanying the loss of nerve fibers.
- Development of methods for detailed three-dimensional photography and mapping of the contours of the optic nervehead and for precise measurement of optic nerve vascularity.
- Indications that glaucoma may affect contrast sensitivity (a specialized test that measures the ability to detect differences between lighter and darker areas) and color vision very early in the course of optic nerve damage. This finding may lead to earlier diagnosis of the disease.
- Treatment of eyes of diabetics having retinopathy by laser photocoagulation that protects against neovascular glaucoma in which new vessels grow on the iris and seal off the filtration angle.
- Demonstration that glaucoma can develop from the breakdown of red blood cells in an intraocular hemorrhage; their membranes, "ghost cells," do not deform sufficiently to squeeze through the aqueous drainage channels and can occlude the trabecular meshwork thereby blocking aqueous humor outflow.

Research Needs and Opportunities

- Information on the epidemiology of glaucoma, its genetic and environmental risk factors (especially the apparently higher incidence and more severe glaucoma seen in blacks than in whites).
- Studies to define better low tension glaucoma, which is poorly understood, and to evaluate its treatment.
- Development of noninvasive devices for monitoring aspects of aqueous humor inflow and outflow and for assessing the health of the optic nerve to aid basic studies of mechanisms underlying glaucoma and enhance treatment of glaucoma.
- Exploration of the causes of failure of glaucoma surgery (closure of the opening created to allow drainage of aqueous humor to the outside of the eye), including the role of aqueous humor factors.
- Studies of the relationship between intraocular pressure and optic nerve damage to determine which patients with ocular hypertension will suffer loss of vision and how to forestall it.
- Development of methods other than intraocular pressure reduction to protect the optic nerve and to reduce or reverse optic nerve damage.
- Controlled clinical trials of laser treatments of the trabecular meshwork to improve aqueous humor outflow in open-angle glaucoma, including establishing criteria for patient eligibilty and defining proper modes of treatment.
- Clinical evaluations of automatic perimeters, devices for mapping the visual field, and development of alternative means for determining the status of visual function in glaucoma patients.
- Refinement of techniques, such as fluorescein photometry, for measuring the rate of aqueous humor formation, that can be used in the clinic.
- Development of new drugs to lower intraocular pressure and new modes of delivering them to specific targets in the eye.
- Pre-clinical studies, especially in monkeys, to apply to glaucoma therapy information about new drugs based upon studies with isolated cells and tissues.
- Continued characterization of the biology of the trabecular meshwork, including its responses to various categories of drugs, the properties of trabecular cells in tissue culture, and how large molecules filling the spaces between cells can impede outflow of aqueous humor.

- Better definitions of the underlying anatomic abnormalities and mechanisms of angle-closure and elucidation of risk factors for predisposition of some narrow-angled eyes to angle-closure glaucoma.
- Evaluation of continuous drug treatment with miotics in preventing angle-closure, and determination of the therapeutic benefit of physically separating the tissues which have overgrown and sealed the angle of the eye.
- Better understanding of congenital and developmental glaucoma by studying the embryonic development of the normal tissues in and surrounding the chamber angle.
- Improved means for evaluating glaucoma in children, especially for accurate noncontact determination of intraocular pressure, and for assessing the effects of anesthetics on these measurements, for measurement of the anterior chamber angle, and for evaluating visual function.
- Development of new drugs and drug delivery systems specifically for children, and initiation of clinical trials to evaluate surgical treatments for glaucoma in children.
- Epidemiologic and natural history studies of the formation of abnormal blood vessels on the iris, often occurring as a severe complication of certain retinal vascular diseases, and the resultant neovascular glaucoma, evaluation of possible predictive factors, and development of improved treatment for this condition.
- Improved treatment of glaucoma secondary to uveitis (inflammation of the eye's middle coat, the uvea), through better understanding of the mechanisms of inflammation, and evaluation of the effectiveness of specific antiinflammatory drugs in its treatment.

Training and Manpower Needs

More highly qualified clinical and academic investigators must be attracted to glaucoma research. Cell biologists, physiologists, and other basic scientists should be encouraged to collaborate with ophthalmologists and to apply their specialized knowledge to the important problems in glaucoma research. It is especially important that more clinicians become involved in clinical research protocol design and clinical trial methodology.

Highlights of Program Development Priorities

- Conducting clinical and laboratory studies to define genetic, racial, and environmental risk factors for the development of damage to the optic nerve in glaucoma and to determine the reasons for the varying susceptibilities of individual eyes to optic nerve damage.
- Developing improved methods of detection and diagnosis and better drug and surgical treatments for glaucoma.
- Devising new noninvasive clinical techniques for studying aqueous humor formation and flow, for continuous monitoring of intraocular pressure in man and in primates, and for studying experimental optic nerve damage in monkeys.
- Studying the cell biology and molecular characteristics of the outflow tissues and their abnormalities in glaucoma, especially using tissue and organ culture techniques.
- Exploiting experimental methods of studying the basic physiology and pharmacology of fluid movement in the eye and of controlling of aqueous humor inflow in primates and in man.
- Investigating neovascular glaucoma and developing methods for its treatment.
- Establishing eye donor programs so that appropriately obtained and preserved human tissues from well-characterized glaucoma patients will become available for correlations between clinical history and tissue damage and for cell biology studies.

Summary Resource Table
(Dollars in Thousands)

Subprograms	FY 1981 Grants*	Cost	Panel Recommendation FY 1983 Add. Grants	Cost	Total Grants	Cost**
1. PRIMARY OPEN-ANGLE GLAUCOMA						
a. Etiology, Epidemiology, Management, and Therapy	7 $723	(8%)	6 $785	(17%)	13 $1,508	(10%)
b. Aqueous Humor Dynamics: Inflow	27 $2,885	(30%)	7 $1,059	(20%)	34 $3,944	(27%)
c. Aqueous Humor Dynamics: Outflow	24 $2,273	(27%)	7 $1,323	(20%)	31 $3,596	(25%)
d. The Optic Nerve	16 $1,771	(18%)	6 $781	(17%)	22 $2,552	(18%)
2. OTHER GLAUCOMAS						
a. Angle-Closure Glaucoma	3 $155	(3%)	3 $541	(9%)	6 $696	(5%)
b. Developmental, Congenital, and Infantile Glaucomas	2 $137	(2%)	3 $443	(9%)	5 $580	(4%)
c. Secondary Glaucomas	11 $836	(12%)	3 $788	(9%)	14 $1,624	(11%)
Total	**90** **$8,780†**	**(100%)**	**35** **$5,720**	**(100%)**	**125** **$14,500**	**(100%)**

* Includes R01, R10, R23, P50, K04, and K07 mechanisms.

** Estimated average cost of grants in Glaucoma program for FY 1983 is $116,000.

† Does not include one conference grant and one grant for scientific evaluation supported by Glaucoma program funds.

STRABISMUS, AMBLYOPIA, AND VISUAL PROCESSING

Introduction

Seeing involves a series of highly complex events which begin the instant light enters the eye and images fall onto the retina and continue until objects are perceived in all their detail, depth, and color. The act of seeing is always accompanied either by purposeful targeted eye movements or by searching and scanning movements. It is further refined by turning the eyes inward (convergence) when looking at any one of the many parts of the elaborate and precisely controlled systems for ocular development, information processing, or eye movements can lead to serious visual impairment such as amblyopia (severely reduced vision in one eye—often called "lazy eye"), strabismus (misalignment of the eyes—cross-eye or walleye), nystagmus (irregular eye movements), myopia (nearsightedness), defects in the field of vision, or other conditions requiring very strong corrective lenses. These conditions collectively affect over 10 percent of the United States population. Although they seldom cause legal blindness they produce considerable visual impairment and disability, interfere with learning and working, and even cause psychological problems because of their effect on appearance.

The NEI Strabismus, Amblyopia, and Visual Processing program supports research on the structure, function, development, and disorders of those portions of the brain and extraocular muscle system that serve vision. These studies are directed toward gaining a better understanding of normal vision as well as determining the causes of visual deficits and blindness that do not appear to be due to specific dysfunction of the eye itself. Understanding visual processing and the disorders that affect it is almost totally intertwined with that of knowledge of how

the human nervous system works. This includes molecular, cellular, genetic, and chemical aspects, how nerve impulses are transmitted and integrated, and the resultant perceptual and motor responses. The continued advancement of clinical investigation of normal and abnormal visual processing depends upon an improved understanding of basic visual mechanisms. Only by supporting both basic and clinical research can new methods be developed for preventing, diagnosing, and treating visual sensory and motor disorders.

Each portion of the visual pathway performs a specific function. The optical elements of the eye, the cornea and lens, focus images on the retina, the photosensensitive surface at the back of the eye. Information transmission through the retina is a complex process, with interactions among elements occurring at each stage. Ganglion cells, the output cells of the retina, have been classified into functionally specialized types, each sensitive to different stimulus sizes, velocities, and locations in the visual field. Projections from these ganglion cells form the optic nerve and optic tract that in turn project to a group of cells in the thalamus of the brain known as the lateral geniculate nucleus. From there nerve impulses are sent to the visual cortex at the back of the brain. The visual cortex is also a complex structure, divided into anatomically distinct layers and functionally separate columns of cells. Some retinal ganglion cell axons send branches into a region of the midbrain known as the superior colliculus, which aids in orientation to objects or other visual stimuli through control of eye movements. Clearly, a major portion of the brain is directly and exclusively involved in the visual process; this is consistent with the very great sensory importance of sight.

Subprograms. The subprogram structure of the Strabismus, Amblyopia, and Visual Processing program, shown below, reflects the NEI's commitment to both basic and clinical research and also serves as the basis for program analysis, evaluation, and planning. It also provides the organization for the planning Panel's complete report (Volume Two, Part Five):

1. **Visual Processing and Amblyopia**
   - a. Normal and Abnormal Development
     - (1) Molecular
     - (2) Cell and Systems
     - (3) Behavior
   - b. Structure and Function
     - (1) Molecular
     - (2) Cell and Systems
     - (3) Behavior
   - c. Disorders
     - (1) Amblyopia
     - (2) Sensory Neuro-Ophthalmic Disorders
2. **Ocular Motility and Strabismus**
   - a. Normal and Abnormal Development
   - b. Structure and Function
     - (1) Conjugate Eye Movements
     - (2) Vergence and Accommodation
     - (3) Muscle Structure and Physiology
   - c. Disorders
     - (1) Strabismus
     - (2) Motor Neuro-Ophthalmic Disorders
3. **Optics and Refractive Errors, Including Myopia**
   - a. Optics and Refractive Errors, Including Myopia

The following are brief descriptions of the three major vision disorders the program addresses:

Amblyopia. Amblyopia, or lazy eye, occurs when the two eyes send different visual information to the brain during infancy, either because of misalignment (strabismus) or differences in the focusing power (refraction) of the two eyes, or occlusion (blocking of the vision in one eye by opacities such as congenital cataract). If this functional blindness in one eye is not corrected during very early childhood, permanent loss of vision in that eye can develop, as it has in at least 2 to 4 percent of the U.S. population.

Strabismus. The eye movement defect known as strabismus (cross-eye or walleye) is the most common cause of amblyopia and is itself seen in 3 to 4 percent of the population. Eye muscle surgery to correct strabismus is the second most frequently performed eye operation in the United States, accounting for 83,000 procedures each year.

Refractive Errors. Because about 60 percent of the population (including an estimated one-fourth who are myopic) wear corrective lenses during all their waking hours, it would be difficult to overestimate the public health importance of refractive disorders or not conclude that they require a considerable research effort.

Although these disorders may not always threaten their victims with total blindness, they can be highly destructive to their quality of life.

Program Goals

- To understand the mechanisms controlling the development of the central visual system, including its modifiability by endogenous and exogenous factors.
- To develop clinically useful, noninvasive methods of assessing visual capacities in adults and, especially, in infants and young children.
- To define at molecular, cell and systems, and behavioral levels the normal and abnormal processing of visual information.

- To use this knowledge to devise better strategies for preventing and treating amblyopia and other neurosensory disorders.
- To understand the development, structure, and function of the neural and muscular systems that control eye movements, including the variety of subsystems involved in fixating and tracking objects and the interaction of the visual and vestibular sensory systems.
- To understand the accommodative process and its relationship to vergence eye movements, especially during infancy and in early childhood disorders of ocular motility.
- To devise better surgical, pharmacological, and behavioral methods for managing strabismus and other neuro-ophthalmological disorders of ocular motility.
- To determine the etiology and course of development of myopia and other refractive errors in order to prevent their occurrence or progression.

Current Support

Support for research in the United States on strabismus, amblyopia, central visual processing, eye movements, and other neuro-ophthalmic disorders is provided mainly by the National Eye Institute. In FY 1981, NEI supported 268 research grants at a total cost of $22.3 million. Additional support for research on basic visual mechanisms was provided by the National Science Foundation, the National Institute of Neurological and Communicative Disorders and Stroke, and the National Institute of Mental Health. Some studies of visual development were supported by the National Institute of Child Health and Human Development. The Department of Defense supported research on basic perceptual processes and their application to combat or flight situations.

Recent Accomplishments

- Development of behavioral techniques that allow measurement of visual function in infants and young children.
- Discovery of a general pattern of progression from more diffuse patterns of neural connections in central pathways during early development to more restricted patterns in adulthood. This is important because it provides testable hypotheses as to how visual experience affects development of the visual system.
- Establishment of an animal model for visual deprivation amblyopia.
- Demonstration that the injection of certain chemicals called biogenic amines may allow the visual cortex to adapt to altered input past the time when this is normally no longer possible. Reversal of amblyopia or binocular dysfunctions may thus be possible at older ages than currently believed.
- Identification of anatomically and functionally distinct pathways from the retina to central visual structures and behavioral evidence that visual information is processed via a limited number of separate channels in the visual system. These discoveries have led to searches for involvement of separate functional pathways in disorders such as amblyopia, multiple sclerosis, and glaucoma rather than a global sensory deficit.
- Confirmation by a variety of new anatomical techniques of the discovery that cells in the visual cortex are organized into ocular dominance columns. These results imply that information from the two eyes is integrated at the cortical level and may be useful in our understanding of such phenomena as binocular suppression or amblyopia resulting from strabismus.
- Development of new techniques for identifying neurotransmitters that are important regulators and intercellular messengers in central visual pathways and identification of at least one inhibitory transmitter (gamma-amino butyric acid, or GABA) in the visual cortex.
- Demonstration that various components of the visual system are differentially susceptible to visual deprivation. This may explain the wide variety of clinical, electrophysiological, and psychophysical responses that are seen in people with amblyopia.
- Demonstration that papilledema (optic nerve swelling) results from a damming of axoplasmic flow (the flow of materials inside the nerve), not from accumulation of intracellular fluid as previously thought.
- Use of a noninvasive technique for studying brain activity evoked by light flashes, known as the visually evoked response (VER), for differential diagnosis of optic neuritis, the ocular aspects of multiple sclerosis, and ischemic optic neuropathy.
- Evidence that the vestibulo-ocular system (the system for maintaining fixation on an object by drawing the eyes in a direction opposite that in which the head is moving) in humans matures earlier than other human oculomotor systems; however, maturation may be significantly delayed in premature infants. These different rates of maturation mean that the systems involved may be more or less susceptible to external

influences at given points in the developmental process.

- Application of control systems analysis to the oculomotor system which will help investigators identify the most important aspects of the system and focus their research on these aspects.
- Discovery of brainstem structures not previously known to be important in the control of eye movements through use of sophisticated tracer and intracellular recording techniques in alert animals.
- New knowledge of the oculomotor aspects of the superior colliculus (a region in the upper midbrain that is concerned with eye movements) and frontal eye fields (regions in the front part of the brain that respond to visual stimuli) may help bridge the gap between the sensory input (seeing) and motor output (eye movement).
- Demonstration that the drug baclofen stops one form of uncontrolled alternating eye movements (nystagmus), emphasizing the importance of neurotransmitter studies of the oculomotor system.
- Experimental use of botulinum toxin to treat strabismus in cases where surgery was contraindicated.
- Identification of a strain of monkey with naturally occurring strabismus which is somewhat comparable to that found in humans.
- Use of quantitative eye movement recordings to characterize congenital nystagmus and a variety of other neuro-ophthalmological disorders.
- Demonstration that prolonged eyelid closure during infancy produces axial myopia in monkeys, tree shrews, and humans.

Research Needs and Opportunities

- Comparison of the ability of visually evoked potential and psychophysical procedures to "dissect" the visual system noninvasively, especially in infants and very young children, to understand better both normal and abnormal visual processing and developing and evaluating additional diagnostic and screening techniques.
- Determination of the interplay among molecular and cellular factors, visual experience, genetics, and temporal factors during visual development.
- Studies of the factors important in regeneration of the optic nerve.
- Studies of the early embryological development of the visual system to gain knowledge that may lead to the ability to repair damage to the optic nerve and visual pathways.
- Further exploration of the concept of a limited number of sensory channels and their relation to underlying neural mechanisms of vision.
- Continued studies of cellular and integrative mechanisms of sensory function using new techniques that permit finer analysis of the underlying anatomy and physiology; analysis of new insights obtained at the cellular level to understand better the functioning of the visual sensory system as a whole.
- Further analysis of the various types of cells within the visual cortex and determination of how each contributes to form vision, eye movements, and other visual functions.
- Further studies of the different cellular columnar systems in the cortex, their relationship to one another, and their role in visual processing.
- Epidemiological studies of sensory neuro-ophthalmic disorders and refractive errors on a worldwide basis to determine possible risk factors that make infants more susceptible to these disorders.
- Continued studies to identify the neurotransmitters used at various levels in the visual pathways and then developing drugs to modify their action in human disorders and experimentally in normal animals.
- Development of appropriate animal models of strabismus to aid understanding of the sensory and motor deficits in this disorder. Developing techniques of visual deprivation in animals that produce moderate defects in visual acuity, but which preserve some degree of binocularity, to simulate more closely the human condition of amblyopia.
- Identification of the critical period during which misalignment of the eyes (strabismus) or opacities can cause a permanent defect of binocular vision.
- Further evaluation of the effects of eye patching or occlusion, a procedure commonly used to treat amblyopia, at different ages on various cellular components of the visual system.
- Development of experimentally-induced primate models of optic neuropathies that will aid in understanding and diagnosing these disorders in humans.
- Development of techniques to analyze eye movements that can be used in newborn nurseries to determine how delays in maturation of the visual system can lead to eye movement disorders.
- Studies of the process whereby the normal infant establishes the ability to use the two eyes together.

- Investigations of how eye movement systems in infants adapt more rapidly than those of adults to compensate for visual cortical damage.
- Tests that could be used in the clinic to distinguish among the various types of eye movements and to detect abnormalities.
- Continued use of anatomical tracers (chemical substances that trace brain activity) in combination with recording brain signals from alert animals, especially primates, to study the roles of the brainstem, cerebellum, and cerebral cortex in eye movements.
- Identification of the neural mechanisms that allow the oculomotor system to adapt to altered visual input.
- Studies of the effectiveness of new surgical, pharmacological, and other nonsurgical treatments for strabismus.
- Continued study of how eye movements are affected in a variety of neurological diseases, with the aim of improving diagnosis and treatment and of providing explanations of these disorders.
- Comparison of the cost-effectiveness of computer-assisted diagnosis of oculomotor functions with clinical analysis by trained neuro-ophthalmologists.
- Studies of the etiology and mechanisms of myopia, using both animal models and physiochemical approaches.
- Development of methods for mass screening for refractive errors.

Research Training Needs

The field of developmental biology has expanded rapidly in the last decade and major breakthroughs have occurred, often in studies of the visual system and particularly in basic scientific studies. It is essential to understand how the visual system matures normally in order to comprehend better ocular sensory and motor abnormalities. A major effort should be made to bring young clinicians with an interest in and knowledge of developmental biology into the field of pediatric ophthalmology. Research fellowship programs in this discipline should be encouraged where there are personnel able to provide such training. A multidisciplinary approach that combines the efforts of basic scientists and clinicians is needed so that the most dynamic and useful approaches to developmental research are applied effectively to clinical problems such as strabismus and amblyopia.

Additional biomedical engineers, ophthalmologists, and optometrists are needed who are familiar with research techniques and who can collaborate with psychophysicists in designing and evaluating improved methods for measuring visual acuity and oculomotor function, particularly in infants and young children.

Epidemiologists are needed to assess the frequency, distribution, and possible causes of both strabismus and myopia. Research ophthalmologists, working with geneticists and epidemiologists who are knowledgeable about the visual system and its disorders, are needed to conduct clinical trials for evaluating various strategies and timing of strabismus treatment.

Also needed are highly trained clinicians who will apply for research grants, especially in the following priority research areas of the Strabismus, Amblyopia, and Visual Processing program. The number of institutions where such clinical research is currently being performed is quite limited; therefore, clinical research training support needs to be directed toward increasing the number of institutions engaged in clinical research as well as the training of individual clinical investigators.

Highlights of Program Development Priorities

- Developing new or improved techniques for treating strabismus, including surgical, pharmacological, or other approaches; evaluating the most promising techniques in controlled trials; and determining how the timing of treatment influences its success.
- Developing and evaluating new treatments for amblyopia, including eye patching, contact lenses, or pharmacological approaches.
- Devising noninvasive methods for studying the development of visual processing in infants, particularly methods that could be used in the clinic for diagnosing and monitoring the effects of treatment.
- Studying the normal development and control of the eye movement system and the disorders that may affect it, especially using techniques that will aid in diagnosing eye muscle problems in newborns and young children.
- Determining the causes of and mechanisms responsible for the development of myopia in humans, expanding studies with animal models, and relating the results of animal studies to the human condition.
- Investigating the structure, function, and development of the visual system at the molecular level—including studies of cellular receptor sites, cell specificity, neurotransmitters and peptides, and immunological approaches—with the ultimate aim of designing drug treatments for visual neurosensory disorders and injuries.

- Studying the anatomy, physiology, and behavior of the systems that are important in vergence (moving the two eyes toward or away from each other to look at a nearby or faraway object) and accommodation (changing the shape of the lens to allow the eye to focus on an object) in normally developing infants as well as in those at risk for strabismus.
- Exploring the etiology of optic neuritis and optic nerve atrophy and those factors that may permit regeneration of the diseased or injured optic nerve.

Summary Resource Table

(Dollars in Thousands)

Subprograms/Areas	FY 1981 Grants* Cost		NAEC Recommendation FY 83 Add. Grants Cost		Total Grants Cost**	
1. VISUAL PROCESSING AND AMBLYOPIA						
a. NORMAL AND ABNORMAL DEVELOPMENT						
(1) Molecular	19 $1,675	(7%)	6 $775	(7%)	25 $2,450	(7%)
(2) Cell and Systems	51 $4,682	(19%)	−7 −$370	−(8%)	44 $4,312	(12%)
(3) Behavior	12 $832	(4%)	4 $736	(5%)	16 $1,568	(5%)
Subtotal	**82** **$7,189**	**(30%)**	**3** **$1,141**	**(4%)**	**85** **$8,330**	**(24%)**
b. STRUCTURE AND FUNCTION						
(1) Molecular	6 $579	(2%)	11 $1,087	(13%)	17 $1,666	(5%)
(2) Cell and Systems	62 $5,212	(23%)	−1 $766	−(1%)	61 $5,978	(17%)
(3) Behavior	38 $2,779	(14%)	−6 $357	−(7%)	32 $3,136	(9%)
Subtotal	**106** **$8,570**	**(40%)**	**4** **$2,210**	**(5%)**	**110** **$10,780**	**(31%)**
c. DISORDERS						
(1) Amblyopia	9 $646	(3%)	15 $1,706	(18%)	24 $2,352	(7%)
(2) Sensory Neuro-Ophthalmic Disorders	1 $74	(1%)	7 $710	(8%)	8 $784	(2%)
Subtotal	**10** **$720**	**(4%)**	**22** **$2,416**	**(26%)**	**32** **$3,136**	**(9%)**
Total	**198** **$16,479**	**(74%)††**	**29** **$5,767**	**(35%)**	**227** **$22,246**	**(64%)**

Subprograms/Areas	FY 1981 Grants Cost*		Panel Recommendation FY 1983 Add. Grants Cost		Total Grants Cost**	
2. OCULAR MOTILITY AND STRABISMUS						
a. NORMAL AND ABNORMAL DEVELOPMENT	5 $439	(2%)	12 $1,227	(14%)	17 $1,666	(5%)
b. STRUCTURE AND FUNCTION						
(1) Conjugate Eye Movements	39 $3,277	(15%)	6 $1,133	(7%)	45 $4,410	(13%)
(2) Vergence and Accommodation	6 $384	(2%)	7 $890	(8%)	13 $1,274	(4%)
(3) Muscle Structure and Physiology	4 $347	(1%)	2 $241	(2%)	6 $588	(2%)
Subtotal	**49** **$4,008**	**(18%)**	**15** **$2,264**	**(17%)**	**64** **$6,272**	**(19%)**
c. DISORDERS						
(1) Strabismus	9 $618	(4%)	15 $1,734	(18%)	24 $2,352	(7%)
(2) Motor Neuro-Ophthalmic Disorders	4 $265	(1%)	5 $617	(6%)	9 $882	(2%)
Subtotal	**13** **$883**	**(5%)**	**20** **$2,351**	**(24%)**	**33** **$3,234**	**(9%)**
Total	**67** **$5,330**	**(25%)**	**47** **$5,842**	**(55%)**	**114** **$11,172**	**(33%)**
3. OPTICS AND REFRACTIVE ERRORS, INCLUDING MYOPIA						
a. OPTICS AND REFRACTIVE ERRORS, INCLUDING MYOPIA	3 $261	(1%)	9 $915	(10%)	12 $1,176	(3%)
TOTAL	**268** **$22,070**	**(100%)**	**85** **$12,524**	**(100%)**	**353** **$34,594**	**($100%)**

* Includes R01, R10, R23, P50, K04, and K07 mechanisms.

** Estimated average cost of grants in Strabismus, Amblyopia, and Visual Processing program for FY 1983 is $98,000.

VISUAL IMPAIRMENT AND ITS REHABILITATION

Introduction

An estimated 10 million Americans have irreversibly impaired vision. About 1.5 million persons are unable to read ordinary newsprint, even with the best possible optical correction, and 500,000 people are classified as being legally blind. Some legally blind individuals are totally blind, but a majority have some usable residual vision and are said to be partially sighted.

A wide diversity of visual characteristics and rehabilitative needs exist among visually impaired persons. Unfortunately, studies of visual impairment and rehabilitation of the affected population have not flourished as has biomedical research in general. As a result, the needs of visually impaired people have not been addressed in a comprehensive fashion.

The visually impaired population includes not only blind people, but also those who are partially sighted. Loss in visual acuity experienced by these people may range from slight to profound; visual field loss may be predominantly peripheral or predominantly central, other visual functions such as dark adaptation, color vision, and contrast sensitivity may be impaired; or there may be increased sensitivity to glare. Handicaps resulting from impaired vision include diminished ability to read, to recognize faces and facial expressions, to perform visually guided motor tasks, to be aware of the important features of one's immediate environment, or to see at night. The extent of the disability created by the visual impairment depends not only on the nature and extent of the visual loss, but also on the needs, aspirations, attitudes, and physical abilities of the individuals.

Although research on the prevention, diagnosis, and treatment of eye diseases and visual disorders offers the best hope for reducing blindness, also needed are studies aimed at helping those who already have irreversibly impaired vision. To meet this need, the National Eye Institute supports research aimed at enabling partially sighted and totally blind people to perform important tasks in school, at the workplace, or in leisure activities. Part of this research is directed at better characterization of the effect of specific diseases on vision, one goal of which is to help people with such problems make the most effective use of their remaining sight. Research is also needed in the design, development, and evaluation of optical aids, video magnification or image enhancement systems, methods for training people with impaired central vision to use their peripheral vision more effectively, and other techniques aimed at improving performance of visual tasks and substituting partially or completely for lost vision.

Program Goals

- To advance research designed to enhance the rehabilitation, training, and quality of life of blind and partially sighted persons.
- To characterize and categorize visual handicaps in terms of functional visual loss.
- To maximize the use of residual vision in partially sighted persons.
- To develop and evaluate devices and procedures to aid blind and partially sighted persons to function independently.

Current Support

The National Eye Institute is a leading source of support for research on visual impairment and its rehabilitation, with 23 related projects supported at a total cost of $1.7 million in 1981. Of these, only two grants, costing a total of $34,000, are concerned primarily with visual impairment; the other research grants are designed to characterize visual functioning in a variety of disorders. Two other NEI grants, at a total cost of $132,000, are directed toward rehabilitation of blind persons.

Some funding for research in visual impairment and its rehabilitation is also provided by several Federal agencies and, to a lesser extent, by state rehabilitation agencies and private organizations. The Federal agencies with a stated interest in funding research in this area include the National Institute of Child Health and Human Development, National Institute on Aging, National Institute of Handicapped Research, National Center for Health Services Research, Bureau for the Blind and Visually Handicapped, Office of Special Education, National Science Foundation, Department of Defense, and the Veterans Administration.

There is a major need to develop, organize, and coordinate research in visual impairment and its rehabilitation, whether supported by NEI or other government or private organizations. Initial steps toward this organization and improved communication are now being taken. Also needed are broadly based programs that offer different research approaches, as well as wide-ranging clinical and basic research training programs.

The current level of support for research on visual impairment and its rehabilitation falls far short of meeting the needs of the hundreds of thousands of Americans who are blind or severely visually impaired.

Recent Accomplishments

- Development of new methods to evaluate visual performance, including improved visual acuity charts, contrast sensitivity measurements, and psychophysical and electrophysiological analyses of the central and peripheral retina.
- Development of several devices useful to individuals with visual loss, including:
  - Spectacle-mounted bioptic telescopes;
  - Monocular telescopes with wide ranges of focus;
  - Use of Fresnel prisms to aid peripheral vision;
  - Improved video magnification systems with adjustable brightness, contrast, and border enhancement;
  - Improved electronic voice synthesis;
  - Laser and sonar-based mobility aids;

- Infrared viewing systems to assist with night vision;
- Instrumentation to convert visual stimuli into tactile signals; and
- Materials that produce raised impressions after the application of pressure which can be used for direct brailling or writing.

Research Needs and Opportunities

The list of research needs below is intentionally more comprehensive than those specifically within the mission of the National Eye Institute. The Council wishes to highlight a broad range of research needs in the fields of visual impairment and its rehabilitation in hope of attracting interest and support by other organizations as well.

- Study visual characteristics (capacities or incapacities) of individuals with impaired vision. In particular, assemble patient groups for effective analysis of visual impairment characteristics (for example, by age, cause of visual loss, or functional abilities lost) and conduct epidemiological studies on these groups. Study the optical and other rehabilitative needs of those with impaired vision who share common visual characteristics.
- Develop special contact lenses and other optical aids for patients with highly irregular corneas or with other severe optical distortions.
- Devise and evaluate different strategies for training those with impaired vision to improve the utilization of their residual vision.
- Study the oculomotor behavior of persons with deficits affecting only part of the visual field to identify potentially helpful eye movement strategies and adaptations.
- Conduct research on the basic skills and senses related to mobility and orientation.
- Develop special and appropriate simulated environments for human engineering studies to aid partially sighted, legally blind, and totally blind individuals.
- Understand the differences in impact of visual impairment on persons in their younger, middle, and later adult years, as well as the impact of an individual's visual impairment on others and on society.
- Determine the economic impacts of visual impairment, particularly with respect to age of onset.
- Determine both the positive and negative effects of technological changes on visually impaired persons.
- Identify attributes of visually impaired persons who are considered successful in life, using a variety of indicators.
- Compare the efficacy of various models of multidisciplinary rehabilitative care for the visually impaired.
- Standardize the methods of evaluating and specifying devices to aid the visually impaired.
- Standardize nomenclatures, classifications, and recording protocols for clinical data on visually impaired persons.

Training and Manpower Needs

Because of the extreme diversity of skills needed to conduct the wide range of research on low vision and rehabilitation described above, it will be necessary to attract and train experts to work in multidisciplinary teams. Training could most effectively take place in a research environment affiliated with a low vision or rehabilitation clinic that has a sufficiently large patient base. It may require coordinated training programs at institutions where there are suitable concentrations of research programs and a diversity of interests. Able young investigators need to be attracted into the field. This might be accomplished through the appropriate use of New Investigator Research Awards or other suitable training mechanisms.

Highlights of Program Development Priorities

- Defining the visual characteristics of individuals with specific types of visual impairment.
- Conducting research on the optical, electronic, and other rehabilitative needs of visually impaired persons.
- Conducting research on improving basic skills relating to mobility and visual orientation in the low vision population.
- Encouraging human engineering studies that will help people with specific impairments to interact more independently with their environment.
- Conducting epidemiological studies of the types and extent of visual impairment resulting from a variety of disorders.
- Developing aids, including contact lenses and other specialized lenses for patients with corneal or lens problems.
- Studying the effects of prior visual experience upon the nature and extent of visual impairment in young children and on their ability to function despite such impairment.

Summary Resource Table
(Dollars in Thousands)

Subprograms	FY 81 Grants* Cost		Panel Recommendation FY 83 Add. Grants† Cost**	Panel Recommendation FY 83 Total Grants Cost**
1. Visual Impairment	2 $34	(50%)		
2. Rehabilitiation	2 $132	(50%)		
Total	**4** **$166**	**(100%)**	**23*** **$2,378**	**27** **$2,794**

RESOURCE REQUIREMENTS

After making a grant-by-grant analysis and assessment of current support in each NEI program, as well as of vision-related research projects supported by other Federal and private organizations, the Council and its planning Panels developed estimates of the numbers of projects that would be required to implement the Program Base and Program Development Priority recommendations in each NEI program in FY 1983 (Table). The dollar value of these projects was then calculated by using estimates of the average cost of a grant for FY 1983 in each program. Cost estimates for FY 1984 and FY 1985 represent approximately a 9 percent increase over the preceding year, including 5 percent for inflation. Because of increasing uncertainties in the annual Federal budget, the Council did not recommend a budget for the final two years covered by the Plan, but intends to revise and extend its estimates periodically.

In making these recommendations, the Council and its consultant Panels took the following factors into consideration in each area of research:

- Degree of relevance to NEI program goals and objectives
- Current level of support
- Recent research accomplishments
- Potential for future development
- Availability of trained manpower
- Likelihood of significant progress over the next three to five years

In the Table, the amounts in parentheses represent the total number and dollar value, actual (FY 1981) or estimated (FY 1982–1985), of NEI research awards—individual Research Project Grants, Small Grants for Pilot Projects, New Investigator Research Awards, Research Career Awards, and Specialized Clinical Research Centers—included within each program. The totals for FY 1981 and FY 1983 have been brought forward from the preceding Summary Resource Tables. In addition to these mechanisms, the total shown for each program includes National Research Service (training) Awards, Core Grants, Research Contracts, Scientific Conference Grants, and other types of research support. (Each of these mechanisms is defined in *Volume Three, Support for Vision Research.*)

The Council's purpose in developing these recommendations is to provide a rational estimate of the resources needed to carry out this research Plan at a reasonable level of activity during the fiscal years 1983–1985 and to set priorities for the expenditure of whatever funds the Congress and the President ultimately make available to the NEI for these years.

TABLE. National Advisory Eye Council Planning Budget for the National Eye Institute by Activity FY 1983–1985

(Amounts in Thousands)[1]

	1981 Actual		1982 Estimate		1983 NAEC Estimate		1984 NAEC Estimate		1985 NAEC Estimate	
	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Extramural Research										
Retinal and Choroidal Diseases		$ 42,322		$ 46,078		$ 62,552		$ 68,502		$ 74,482
	(381)	(33,577)	(395)	(36,085)	(492)	(51,660)	(515)	(56,574)	(535)	(61,513)
Corneal Diseases		16,769		17,803		25,085		27,472		29,869
	(162)	(15,849)	(167)	(17,020)	(215)	(23,005)	(225)	(25,194)	(230)	(27,392)
Cataract		9,723		10,651		16,356		17,912		19,475
	(101)	(8,970)	(106)	(10,092)	(137)	(14,796)	(140)	(16,204)	(150)	(17,618)
Glaucoma		9,950		10,865		16,540		18,114		19,694
	(90)	(8,780)	(98)	(9,843)	(125)	(14,500)	(130)	(15,880)	(135)	(17,265)
Strabismus, Amblyopia, and Visual Processing		23,125		22,527		36,744		40,240		43,752
	(268)	(22,070)	(258)	(21,620)	(353)	(34,594)	(370)	(37,885)	(380)	(41,192)
Visual Impairment and Its Rehabilitation		166[2]		513[2]		2,794		3,060		3,328
	(4)	(166)	(5)	(513)	(27)	(2,794)	(30)	(3,060)	(30)	(3,328)
Subtotal, Extramural Research		**$101,889**		**$107,924**		**$160,071**		**$175,300**		**$190,600**
	(1,006)	**(89,412)**	**(1,029)**	**(95,173)**	**(1,349)**	**(141,349)**	**(1,410)**	**(154,797)**	**(1,460)**	**(168,308)**
Intramural Research										
NEI Laboratory and Clinical Research		6,346		6,544		8,275		8,900		9,600
Office of Biometry and Epidemiology		686		750		825		900		1,000
NIH Management Fund[3]		4,543		5,111		5,900		6,400		6,900
Subtotal, Intramural Research		**11,575**		**12,405**		**15,000**		**16,200**		**17,500**
Direct Operations										
NEI Extramural Management		1,657		2,144		2,587		2,800		3,000
NEI Program Management[4]		1,345		1,533		1,800		1,900		2,000
NIH Management Fund[5]		1,260		1,368		1,713		1,800		1,900
Subtotal, Direct Operations		**4,262**		**5,045**		**6,100**		**6,500**		**6,900**
Construction		—		2,000		10,000		10,000		10,000
Total, NEI		**$117,726**		**$127,374**		**$191,171**		**$208,000**		**$225,000**

[1] Numbers in parentheses indicate the total number and amount for individual Research Project Grants, Small Grants for Pilot Projects, New Investigator Research Awards, Research Career Awards, and Specialized Clinical Research Centers included within each program estimate.

[2] No specific appropriation is currently authorized for Visual Impairment and Its Rehabilitation. Grants funded in this area are paid from whichever of the preceding five programs seems most appropriate to the purpose of a given study, usually either the Retinal and Choroidal Diseases program or the Strabismus, Amblyopia, and Visual Processing program.

[3] This portion of the Management Fund is an assessment for NIH central services that support research conducted at the NIH campus in Bethesda, Maryland. These services include operation of the NIH Clinical Center, engineering services, utilities, computer services, and other research services.

[4] Supports the NEI Office of Director and overall NEI management.

[5] This portion of the Management Fund is an assessment for NIH central services that support the general management and program direction of the NEI. These services include central NIH receipt and review of research grant applications, centralized NIH financial management, and other administrative services.

3

IMPLEMENTATION OF PROGRAM PRIORITIES

INVESTIGATOR-INITIATED RESEARCH

A HALLMARK OF the NEI program since its establishment has been its primary reliance on investigator-initiated research and emphasis on the individual NIH research project grant (designated R01) as the mainstay mechanism of research support. Over the years this strategy has proved to be remarkably successful in encouraging creativity and maintaining scientific freedom while assuring a high level of quality in the research NEI supports. Yet, this approach presents a problem in implementing program planning: how can one hope to plan a program that depends so heavily on the initiative of hundreds of independent and geographically dispersed scientists?

While it is acknowledged that the exact ingredients for scientific discovery cannot be specified, the Council believes that an attempt can be made with the aid of experts to plan and evaluate a scientific program by defining long-term goals and objectives, reviewing recent accomplishments, and assessing the state of the art. Currently promising areas of research can be examined and thoughtful conclusions reached about which approaches offer the greatest chance of success and thus ought to be assigned priority in funding over the next few years. Subsequently, progress toward the achievement of program goals and objectives can be monitored, and, keeping abreast of changing research needs and opportunities, priorities can periodically be reassessed and redefined as necessary.

If in developing this Plan the Council has succeeded in preparing a report that adequately outlines the major needs and opportunities that exist in vision research today, and as far as anyone can now foresee, over the next five years, there is good reason to expect that the scientific community will respond favorably to its recommendations. However, implementation of the Plan will not be left to chance; several steps will be taken to help ensure its fulfillment. These include, for the NEI staff:

- Distributing the Plan widely to members of the vision research community, other interested scientists, government officials, and the public and disseminating information about the Plan by mail and through scientific publications.
- Using the Plan's recommendations in making funding decisions.
- Encouraging coordination among various government and private agencies supporting vision research.
- Preparing announcements for publication in the *NIH Guide* and issuing Requests for Applications and Requests for Proposals that solicit grant applications and contract proposals for research in specific priority areas identified in the Plan.
- Working with individual investigators to encourage the submission of grant applications in priority areas.
- Making presentations that highlight the Plan's recommendations and staffing information booths at scientific meetings.
- Organizing workshops and symposia on topics identified in the Plan that could benefit from more in-depth and cross-discipline discussions and publishing their proceedings.
- Helping establish specialized research resources, such as animal colonies.

- Tracking the Plan's implementation by means of a computerized data system and making regular reports thereof to the NEI Director, the Council, and the scientific community.

As for the Council, it can help carry out the Plan by exercising its official mandate to judge the program relevance of individual grant applications. The Council can and does exercise this option. (See Chapter 1, "Introduction" for a full discussion of this process.)

In the balance of this chapter, the Council presents its views on various research issues and administrative support mechanisms other than research project grants available to the NEI in carrying out its mission and implementing the goals, objectives, and priorities set forth in this Plan. They are as follows:

- Clinical Research
- Research Training and Career Development
- Scientific Workshops
- Core Grants and Specialized Clinical Research Centers
- Construction of Vision Research Facilities
- Specialized Research Resources
- Research Contracts
- Intramural Research
- Knowledge Transfer and Information Dissemination
- Role of the NEI in International Prevention of Blindness

Again, although the full range of NIH research support mechanisms is available to the NEI, the Council recommends that the Institute continue to rely primarily on the individual investigator-initiated research project grant (R01) as its primary funding instrument.

CLINICAL RESEARCH

One of the National Advisory Eye Council's primary interests is to encourage more clinical research on diseases of the eye and visual system. Clinical research has been defined by the National Research Council (NRC) as "research on patients; on samples derived from patients as part of a study on the causes, mechanisms, diagnosis, treatment, prevention, and control of disease; or on laboratory animals by scientists identifiable as clinical investigators on the basis of their other work."[1] The NRC also stated that "an essential aim of clinical investigation is to translate new knowledge, through applied research, into new technology and modes of treatment, as well as the validation of new technology through clinical trials." The Council endorses this definition as it applies to vision research.

The support of well-designed, scientifically sound clinical and epidemiological research has been a priority of both the Council and the NEI since their establishment.

This Plan cites many needs for clinical studies and lists several among the priorities in each program. These recommendations are based on a consensus of advisors to the Council concerning the urgency with which certain current clinical research problems must be solved. In reaching their consensus these advisors considered the urgency of these problems, whether enough scientific information existed for the development of sound research hypotheses, and whether sufficient trained manpower was available for carrying out studies to test them.

Development of Hypotheses for Clinical Research

Clinical research must always be based upon careful observations that lead to the formulation of specific hypotheses to be tested. Then protocols must be carefully developed to gather data appropriately.

The Council recognizes that hypotheses for clinical research are developed in many ways. Often they are formulated as a result of clinical observations made during an ongoing experiment or routine clinical examination. Hypotheses may also derive from chance observations in the laboratory, either by basic scientists who are knowledgeable about clinical problems, or by clinicians trained to recognize the clinical implications of laboratory findings.

Clinical research hypotheses also may be based on the results of laboratory experiments deliberately designed to investigate in animals a problem with clinical relevance, for example, laboratory studies of diabetic cataracts in mice. More than a decade ago, scientists discovered that the enzyme aldose reductase triggers cataract development in diabetic laboratory animals. Subsequently, a series of aldose reductase inhibitors capable of delaying or blocking cataract formation was developed. This research has led to several potential clinical applications.

If a suitable animal model or other testing system is available, it is sometimes possible to test immediately in the laboratory a hypothesis resulting from initial observations in the clinic. However, when no satisfactory animal model nor alternative laboratory testing system exists, clinical hypotheses must be tested in the clinic. In the case of proposed new treatment or diagnostic methods, after additional insights are acquired through pilot studies, these

hypotheses must then be assessed in controlled trials in patients and/or normal volunteers if definitive conclusions about a procedure's safety and efficacy are to be made. For example, new medical or surgical treatments for diabetic retinopathy, or for glaucoma, must be evaluated in patients because no adequate animal models of these diseases are available.

The important thing is that no matter what the origin of a clinical research hypothesis, once it is developed, the use of rigorous scientific methodology in testing it is essential. The NEI uses the following criteria to determine whether a proposal for a clinical study should be considered for support:

- Is there a sound rationale for doing the study?
- Does it ask a clinically important question?
- Is the experiment designed to answer the question?
- Are the procedures, protocols, and analyses adequate to ensure acceptance of study findings?
- Are the rights and welfare of participants adequately protected?

Although there is no way to plan the actual development of a specific clinical research hypothesis, it is possible to enhance the clinical environment to make it more conducive to engendering creative thinking which is the essence of hypothesis development. The following are features of a clinical environment in which such creativity can flourish:

1. Exposure to many kinds of patients and clinical problems.
2. Existence of a critical mass of interacting senior, mid-level, and junior clinicians and researchers.
3. Formal and informal workshops and forums for discussing research.
4. Opportunities for interdisciplinary approaches and contacts, including laboratory and biostatistical sciences.
5. Time to be creative. (This includes not being overburdened with clinical care responsibilities.)

Characteristics of Clinical Research

The Council recognizes that there are several special characteristics of clinical research that make it difficult and must be kept in mind when recommending that the solution of certain problems be given priority. First, there is the need to design an ethical protocol that ensures the safety and rights of patients while adhering to rigorous scientific methods. Second, it is often difficult to recruit an adequate number of patients with specific disease characteristics. Third, quality control of data collection and patient compliance with any prescribed regimen must be assured. Fourth, because clinical research may entail a long-term group effort, the organization and management of such studies can become quite complex. Finally, such studies can be expensive.

Types of Clinical Research

Clinical research can take several forms:

- Case reports of systematic observations of one or more patients.
- Parallel studies of humans and animal models of human disease.
- Prospective pilot studies to gather preliminary data.
- Natural history studies in groups of patients.
- Case-control studies.
- Research on improved methods of diagnosis.
- Development of technology including instruments and techniques for clinical diagnosis and treatment.
- Single clinic controlled clinical studies.
- Large-scale, multicenter, collaborative clinical trials.

At present, the greatest needs for clinical vision research are to study systematically the natural history of a number of diseases, especially cataract, macular degeneration, glaucoma, and diabetic retinopathy; to determine risk factors through careful case-control studies and prospective cohort studies; and to develop improved methods of diagnosis, particularly early diagnosis. Clinical trials are needed also to assess new medical or surgical procedures. These needs are outlined in greater detail in *Volume Two.*

Clinical Research Training

Clinical investigators supported by the NEI are generally M.D.s, O.D.s, or professionals who hold other health related doctorates. Although basic scientists often play a vital role in clinical investigation, there is a great need for the clinician-investigator who is uniquely trained to recognize opportunities for research on human disease and to formulate, design, and carry out projects related to these opportunities. In addition, legal, ethical, and regulatory constraints make the clinician's role primary in clinical investigation.

The strength of the NEI's commitment to supporting clinicians in research is indicated in part by the fact that approximately one-third of all research

grants awarded by the NEI over the past five years have had ophthalmologists or other M.D.s as principal investigators. Also, approximately 50 percent of all NEI extramural funds are awarded to ophthalmology departments or divisions in medical schools or to vision research centers.

To be capable of dealing successfully with the difficulties inherent in clinical research—scientific, statistical, ethical, managerial, and financial problems; patient recruitment; quality control of data collection; and patient compliance—clinicians must obtain special training in research methodology. Such training should make a clear distinction between the routine collection of data in patient care and the collection of research data. In particular, it is necessary to learn how to write a research protocol that specifies procedures for data collection and analyses that will ensure that the information collected is adequate in quality and scope for answering the questions posed by the study.

Training in clinical research methodology can be accomplished in a number of ways. One way is for a clinician to assist an established investigator in preparing a proposal for a clinical study. He or she can thereby learn the methodology by which scientific experiments are designed and conducted to follow the natural course of disease, to determine risk factors either through prospective or retrospective studies, or to assess new medical or surgical treatments through clinical trials.

It is also possible for a clinician to learn research methodology by becoming involved in an ongoing, well-designed clinical research project which is properly structured, has a hypothesis to test, and follows a detailed written protocol. The Diabetic Retinopathy Study, the Diabetic Retinopathy Vitrectomy Study, and the Early Treatment Diabetic Retinopathy Study are examples of NEI-initiated studies that have served as models for the design of several other subsequent clinical and epidemiological research projects, most of which, like the ongoing multicenter Macular Photocoagulation Study, have been investigator-initiated. An unexpected but welcome outcome of these studies is that several ophthalmologists who have participated in them, and who were thereby involved for the first time in the conduct of a clinical trial, have subsequently applied clinical trial principles and methods to their own research interests and have been successful in competing for NEI research grants. In the accompanying list of clinical trials that the NEI funded in FY 1981, all but the first three, which were supported by contracts, were supported through research project grants.

A final way for a clinician to learn research methods and techniques is to spend time in a laboratory in which experiments with animals or tissues are being conducted and in which the variables inherent in an experimental design are well-controlled. In this setting, the scientific method can be learned under "purer" conditions than may be possible in the clinic. Of course, application of the scientific method to the clinic must take into account the additional ethical and logistical aspects of studies involving human subjects.

Clinical Trials Supported by NEI in FY 1981

1. Diabetic Retinopathy Study (multicenter)
2. Diabetic Retinopathy Vitrectomy Study (multicenter)
3. Early Treatment Diabetic Retinopathy Study (multicenter)
4. Branch Vein Occlusion Collaborative Study (multicenter)
5. Macular Photocoagulation Study (multicenter)
6. Prospective Evaluation of Radial Keratotomy (multicenter)
7. Photocoagulation Studies on Retinal Vein Occlusion
8. Prematurity, Vitamin E, and Retrolental Fibroplasia
9. Tocopherol Protection in Retinopathy of Prematurity
10. Retrolental Fibroplasia: Clinical and Research Aspects
11. Histocompatibility (HLA) Antigens in Keratoplasty
12. Contact Lens Effects on Refractive Error
13. Ascorbic Acid Therapy in Alkali Burns of the Eye
14. Cataract Management—A Randomized Controlled Trial
15. Timolol: A New Drug for the Treatment of Glaucoma
16. Glaucoma Clinical Research Center *
17. Carbonic Anhydrase Inhibitors in Treating Glaucoma
18. Chemical Alteration of Extraocular Muscle Function
19. Human Applications of Basic Eye Position Mechanics

* Clinical trial portion of this Center (P50) award.

Research training should last for a period of at least one year, although two years are preferable. For clinicians, this period may either precede, coincide with, or follow resident clinical training. In some cases it may be desirable to extend the training period to provide the clinician with an opportunity to acquire preliminary data that may serve as the basis for a full-scale clinical research project. One indication of the quality of an individual's clinical research training is the trainee's subsequent success in competing for research grant support from the National Eye Institute or other Institutes at the National Institutes of Health.

An ideal clinical training facility should have examining rooms dedicated to research and laboratories adjacent to patient care areas (for example, laboratories for psychophysical testing, electrodiagnostic procedures, histology, and chemistry). There should be excellent photographic facilities with personnel capable of taking high quality photographs by which patients' conditions can be closely followed. The investigator must be willing to commit the necessary amount of time to carry out the goals of the clinical research. Clinic coordin-

ators and allied health personnel should be accessible, and statistical collaboration or consultation should be available from the initiation of the design phase of a clinical research project to final data analysis.

NEI Research Training Support

The manpower to conduct needed clinical studies is quite limited. This fact has serious implications for disease-oriented vision research, because whole areas are without an adequate base for clinical investigation. Therefore, the NEI has taken a number of steps to encourage the training of clinical investigators and the further development of clinical research. These are discussed in the following section on Research Training and Career Development.

Recommendations

The Council strongly encourages more clinicians to become involved in clinical research either by participating in ongoing studies at their institutions or by undertaking formal research training. In addition, the Council encourages the NEI staff to continue its plans to create a Clinical Protocol Development Grant to assist investigators in developing multicenter collaborative clinical projects, particularly those outlined in the Program Development Priorities identified in *Volume Two* of this Plan. These grants are envisioned as one-year, one-time awards for the development of a research protocol and manual of procedures. When these materials are prepared, they can then be submitted to NIH for the usual peer review. As a further step to encourage both clinical research training and clinical research, because the staff of clinical departments are often not aware of what NEI resources are available to them, the NEI should develop printed materials which explain clearly the array of support mechanisms available for this purpose.

RESEARCH TRAINING AND CAREER DEVELOPMENT

Background

In 1974, the Congress enacted new training legislation, the National Research Service Award Act, which mandated that a continuous supply of well-trained scientists be available to carry out the research necessary to meet national health goals. The Act requires that the Nation's personnel needs for biomedical and behavioral research scientists be met through Federal financial support of trainees. Training grant and fellowship mechanisms that had existed prior to the Act were discontinued, and two new National Research Service Award programs were authorized: Individual Postdoctoral Research Fellowships and Institutional Fellowships (training grants). The Act also provided for a national study to establish the qualitative and quantitative needs for biomedical research personnel. The then Department of Health, Education, and Welfare contracted with the National Academy of Sciences to conduct such a study, which has subsequently evolved into an ongoing examination of the Nation's needs for trained biomedical and behavioral scientists.

The National Advisory Eye Council recognizes that the future of research generally, and of vision research in particular, depends upon the availability and continuous replenishment of the supply of well-trained investigators. There is evidence that trainees with Federal support are able to complete their training more effectively and more quickly than those without such support. Postdoctoral trainees are able to begin their research careers earlier as a result of their advanced training. The Council also believes that Federal responsibility in research manpower development is not limited to the initial training of those with little or no research exposure, but also includes the further career development of newly trained and experienced investigators alike.

Research Training

At present, support by the National Eye Institute for research training is provided primarily under the following mechanisms. The total number of awards made in each category for the years FY 1977 to FY 1981 is shown in the Table.

1. Individual National Research Service Awards (F32)—Awarded to individual applicants for up to three years of support of postdoctoral research training in laboratory and clinical sciences related to eye diseases and disorders of the visual system.

2. Institutional Grants for National Research Service Awards (T32)—Awarded to institutions to support research training programs that provide opportunities for individuals who wish to pursue research careers in the clinical and laboratory sciences related to vision and disorders of the visual system. These grants primarily are designed to support postdoctoral research and pre- and postresidency research training; however, a limited number of predoctoral positions are also supported.

One controversial aspect of the NRSA program as originally designed was its payback provision, the requirement that for every year of research training, a research fellow must serve a year in a full-time

National Eye Institute
Research Training and Career Development Awards, FY 1977-1981

Fiscal Year	Individual National Research Service Award (F22, F32)		Institutional National Research Service Award (T32)		Academic Investigator Award (K07)*		Research Career Development Award (K04)	
	Number	Cost	Number	Cost	Number	Cost	Number	Cost
1977	105	$1,204,757	43	$2,440,167	18	$462,902	43	$1,369,351
1978	96	$1,168,520	44	$2,834,498	20	$571,304	55	$1,885,099
1979	107	$1,364,103	49	$3,226,098	22	$628,759	56	$2,063,378
1980	128	$1,766,871	42	$2,737,846	18	$577,654	52	$1,854,929
1981	76	$1,418,087	35	$2,510,947	9	$305,921	50	$1,834,198

*The K07 award is no longer being made. This mechanism was converted to R23, the New Investigator Research Award.

academic research or teaching position. In 1981, the Congress changed the law to exempt up to one full year from the payback requirement.

This may help in addressing a major problem: the overall decline in the number of physicians entering research training programs. While the number of ophthalmologists and other M.D.s receiving research grant support from the NEI has actually increased over the past five years, relatively few M.D.s are trained each year under the NEI's NRSA program; currently, they average about 10 percent of the total number of NEI research trainees each year.

The Council recognizes that participation in a formal training program as required under the NRSA provisions is not the only avenue available to clinicians wishing to pursue a research career. As noted in the preceding section, clinicians may learn research techniques by working with established clinical investigators. A number of clinicians who are now engaged in clinical vision research as independent investigators were first exposed to research methodology as participants in NEI-supported clinical trials such as the nationwide Diabetic Retinopathy Study. Yet, the Council thinks it would be desirable if more clinicians interested in research could receive NEI support for at least some time spent in a structured research training environment. To this end, the NEI has taken several steps to encourage clinicians to apply for training awards, including the issuance of program announcements highlighting the Institute's interest in receiving applications for research training in fields particularly suited to clinical investigation: immunology, genetics, pharmacology, epidemiology, biostatistics, physiology, biochemistry, developmental biology, experimental and clinical pathology, psychophysics, and physiological optics. (The latter two categories are emphasized particularly in hope of attracting more optometrists to vision research.) In addition, members of the NEI staff have made presentations to the staffs of academic clinical departments to discuss training and career development opportunities and have held grants "clinics" at such national forums as the annual meeting of the American Academy of Ophthalmology and of the American Academy of Optometry.

Support for clinical research training is also provided through the NEI intramural program by means of the NIH Medical Staff Fellowship Program. Three fellows are selected each year from candidates who have completed a three-year ophthalmology residency program. Fellows are appointed for two years and spend time in both clinical and laboratory research including patient care activities. The NIH Visiting Program offers scientists at all levels of their careers the opportunity to spend time at NIH to receive further training or to conduct research in their area of specialty. The Visiting Fellow award provides advanced training for those with a doctoral degree or equivalent in a health science field and not more than three years of postdoctoral experience. Initial awards are made for one year with the possibility of renewal for up to two years. In addition, one may apply for Individual National Research Service Awards (F32) for training in the NIH intramural program in Bethesda, Maryland.

Research Career Development

For investigators who have completed their training, several grant mechanisms are available to support research and continued career development. The number of awards made in the years FY 1977 to FY 1981 in each of the mechanisms that then existed are shown in the Table. These are:

1. New Investigator Research Awards (R23) [formerly Academic Investigator Awards (K07)]—To foster the further development of newly trained laboratory scientists and clinicians for careers as independent investigators in basic and applied vision science. These awards are made for up to three years and are not renewable, although the investigator may seek continued research support under a regular research project grant (RO1).

2. Small Grants Program for Pilot Projects (R03)—A one-year, nonrenewable award intended to provide support for pilot projects, testing of new techniques, or feasibility studies of innovative and high-risk research, which would provide a basis for more extended research.

3. Research Career Development Awards (K04)—To assist the further development of research careers of newly trained scientists who have demonstrated potential for independent research in vision and ophthalmology. These salary awards are made for up to five years to investigators who already hold an active NEI research grant with three years remaining or who will hold one at the time the career award is made.

In addition, it is important to note that newly trained investigators historically have fared extremely well in competing for regular NIH Research Project Grants (R01). Over the past six years over 40 percent of *all* competing grants awarded by the NEI went to investigators who never before held an NIH research grant; an average of 71 percent of all *new* grant awards went to new investigators.

Previous Recommendations

In the Council's 1978–1982 research Plan, a special Panel considered vision research training and career development needs in detail and made a number of general and specific recommendations. The Panel reaffirmed the need to maintain high standards of excellence in training and career development programs and to maintain a stable, consistent policy in this area. Also, the continued support of training and career development in both the basic and clinical sciences was endorsed. The following is a list of the Panel's specific recommendations, which were written in 1977, and an indication of what responses have been made to them since the Plan was published:

1. Need for Individual Fellowships—The Plan cited the long delays that then existed between the time an application for an NEI individual fellowship was submitted and the actual award. It recommended that the processing of such applications be sped up. In 1978, legislative action eliminated the need for Council review of fellowship applications, and the NIH established special study sections which meet a month earlier than other study sections to review fellowships exclusively. A committee of the NEI staff now performs the secondary level review of fellowships. These actions have reduced the time between application and award from 9 to 12 months to 4 to 6 months.

2. Need for Clinical Investigators—The Council recommended removing the limitation that no more than six Academic Investigator Awards be awarded per year, that the limitation of one award per institution be removed, and that institutions be required to guarantee a faculty position for the awardee only for the period of the award. Subsequently, the limitation in total awards and awards per institution and the faculty position requirement were removed from this mechanism, which is now called the New Investigator Research Award. Also cited was the need for a mechanism to support advanced clinical training in "specific areas where clinical problems can be delineated and where attention can be paid to the development and evaluation of new methods of diagnosis and treatment." The NEI feels that this need can be met through existing mechanisms for support of clinical research, research training, and career development and particularly through the NIH Senior Postdoctoral Fellowship (F33) (see *Recommendations*).

3. Need for Initial Research Support for New Investigators—The Council cited the inadequacies of the Special Visual Sciences Research Awards, which were limited to $10,000 per year and for which there had been few applications. These awards were subsequently phased out and replaced by the New Investigator Research Award (R23) which provides support up to approximately $35,000 per year, with a total award limitation of $107,500 over a three-year period. In addition, a new Small Grants Program for Pilot Projects (R03) was inaugurated in FY 1982. The initial response to this program has been excellent, and this mechanism should offer another opportunity for the new investigator, the clinician with limited research experience, those re-entering research or changing fields, and those at minority institutions to participate in NEI programs.

4. Need to Consider Program Emphasis—The Council stressed the need for emphasizing training which leads to disease prevention. Although no specific mechanism was established for this purpose,

the NEI has placed increased emphasis on all program activities related to prevention of eye diseases or their harmful outcomes (see Chapter 4, "Cross-Cutting Areas and Issues").

5. Need for New Administrative Arrangement—The Council cited the problems inherent in having inflexible, separate NEI budget categories for training and research grants. However, this separation is mandated by the Administration and the Congress and is unlikely to be changed in the near future.

Recent Actions

At its January 1983 meeting the Council adopted the following new guidelines for NEI training programs:

1. The funds available for research training should be allocated approximately equally to the F32 and T32 mechanisms.

2. There should be one date each year for Council review of T32 applications—the September Council meeting. (F32 applications will continue to be accepted for each of the three existing annual deadlines.)

3. In general, T32 grant applications with fewer than five approved slots for postdoctoral trainees will probably not be funded.

4. No more than one training grant will be made to an institution (or, for multicampus institutions, no more than one to each campus). Applications for joint training programs may be submitted by neighboring institutions.

5. The duration of training for each trainee must be at least 12 months and preferably two years.

6. The primary goal of the T32 training grant will be the training of clinical investigators and of basic investigators working in clinically relevant or disease-oriented research.

7. The NEI should continue to foster the development of unique and innovative approaches to research training in specialized areas which specifically require the development or attraction of new vision researchers.

8. Because the implementation of the recommendations above may have an adverse effect on predoctoral training in the vision sciences, the NEI should continue to use the T32 mechanism to support predoctoral training at appropriate institutions, even in the absence of a postdoctoral T32. As a rule, however, the number of predoctoral trainees to be allowed under NEI T32 support at any institution should not exceed the number of NEI postdoctoral trainees under combined F32 and T32 support.

Recommendations

The Council recommends that clinicians in particular be encouraged to apply for research training awards. In addition, clinicians are urged to participate in ongoing clinical research projects and then to apply for initial research support from the NEI, either through the conventional research project grant (R01), the New Investigator Research Award (R23), or the Small Grants for Pilot Projects (R03).

As a further means of encouraging clinical research training, the Council recommends that the NEI promote two infrequently used NEI support mechanisms to provide assistance both to prospective clinical researchers and to those already trained who wish to change fields. These are:

1. Institutional Awards for Short-Term Training (T35)—To provide training support to students in schools of medicine, optometry, osteopathy, dentistry, veterinary medicine, pharmacy, and podiatry for up to three months, rather than the one year or more provided by the T32 program. No payback is required, and between 4 and 32 students per year can be supported for every year of the award in one or more disciplines or departments of the institution receiving the award. This mechanism may be used to support research training during the summer.

2. Senior Postdoctoral Fellowship (F33)—To provide those who have doctoral degrees and at least seven years of professional experience the opportunity to make major changes in the direction of their research careers, to broaden their scientific background, to acquire new research capabilities, and/or enlarge their command of an allied research field. Senior fellowships are usually awarded for a period of 12 months with a limit of 24 months.

SCIENTIFIC WORKSHOPS

Progress in vision research is fostered by frequent exchanges of scientific information and techniques among investigators in this field and between vision researchers and scientists in other fields. Such exchanges occur in the usual course of scientific collaboration, communication, meetings, and publications.

The National Eye Institute has employed the scientific workshop as a mechanism for implementing the National Plans. The focus in these workshops has usually been a vision research area in great need of new scientific approaches and ideas or of a multidisciplinary approach toward resolving that need. For example, a series of three workshops was held in response to recommendations made in the 1978-1982 Plan for more research on the

immunological aspects of ocular diseases and for the application of new knowledge in the field of immunology to the study the visual system.

The first workshop, "Immunogenetics and Transplantation Immunity," held in 1979, led to the identification of several ways in which recent advances in immunogenetics and transplantation immunology might be productively applied to eye research. The second workshop, "Autoimmune Phenomena and Ocular Disorders," identified promising avenues for additional research on the immunological mechanisms which govern autoimmunity in relation to specific ocular diseases. The third workshop, "Immunological Aspects of Ocular Diseases: Infection, Inflammation, and Allergy," examined ways to minimize the destructive effects of inflammation associated with ocular diseases while maximizing the protective effects of the inflammatory process.

Similarly, in response to needs identified in prior program Plans, the NEI has held workshops on such topics as the role of the retinal pigment epithelium in the health and degeneration of the retina and on culture of ocular tissues. The accomplishments arising from these workshops are documented in the various sections of this National Plan and are evidenced by the burgeoning levels of activity and success which have developed in these fields.

NEI workshops are thus an extension of the program planning process. Although the present National Plan has been developed with the advice and assistance of more than 350 experts in vision research, there are areas of scientific need which require more thorough analysis and there are types of scientists whose expertise has not yet been fully tapped. Future workshops will be held to expand, amplify, and make more explicit the statements of needs and priorities in specific areas.

CORE GRANTS AND SPECIALIZED CLINICAL RESEARCH CENTERS

Vision research center grants help bring together the activities of a number of investigators at an institution who share common goals in vision research. The National Eye Institute currently employs two center grant mechanisms: the Core Grant (P30) and the Specialized Clinical Research Center (P50). Until 1973, the NEI also supported Research Program Projects (P01), but these were phased out because the NEI and the National Advisory Eye Council agreed that priority should be given to individual research project grants, each competing on its own merits. This policy also had an impact on Core Grants and Specialized Clinical Research Center awards.

Core Grants (P30)

The intent of the Core Grant is to help maintain institutional environments which foster high quality collaborative research and multidisciplinary approaches to problems of interest to the NEI. The program has two objectives:

- To afford groups of established investigators greater capability for collaborative research by providing them with shared research resources.
- To attract scientists of diverse disciplines (fundamental and clinical) to vision research and to foster their interaction and collaboration.

Shared resources provided by Core Grants are usually grouped into research support modules intended to foster scientific accomplishment beyond that attainable solely with support from individual project grants. Research support modules can be laboratory or clinical research facilities, services, or resources which are used frequently by a number of investigators receiving individual NEI project grant support in complementary areas. Some examples of research support modules are: electron microscope facility, tissue culture facility, electrophysiology unit, patient coordination unit, data processing facility, and biostatistical services. They are directed by investigators who are experts in such areas.

In 1981, the NEI supported 25 Core Grants; this program utilized less than 4 percent of the NEI's research program funds.

Specialized Clinical Research Centers (P50)

A Specialized Clinical Research Center is a place where research is conducted on a specific human eye problem. The emphasis at these centers is on investigations with humans, most often involving the application of recent laboratory findings to human disease problems on an outpatient basis. The types of projects conducted are usually those which would not be practical to pursue outside the Center environment.

A Specialized Clinical Research Center grant provides support for a group of clinical studies which have a common focus on the etiology, pathogenesis, diagnosis, or treatment of human visual disorders. Such studies also must have common requirements, such as specific groups of patients or special clinical research facilities. Specialized Clinical Research Center grants may provide support for both individual clinical research

projects and for core resources if the latter are utilized exclusively in those projects.

The NEI uses this funding mechanism only under exceptional, well-defined circumstances. In 1981, three such Centers received NEI support: two were studying patients with hereditary retinal degenerations and one emphasized the treatment of autoimmune ocular disease.

CONSTRUCTION OF VISION RESEARCH FACILITIES

Nationwide, vision research has developed in large part since 1968 when the National Eye Institute was established. For the National Institutes of Health as a whole, the principal growth period was in the 1950s and 1960s, and the increase in research support was matched by an NIH investment throughout the U.S. of several hundred million dollars in the construction of research facilities. Although the number of NEI-supported grants has increased from 200 in FY 1970 to 1,100 in FY 1981, according to a spokesman for Research to Prevent Blindness, Inc., "With few exceptions [eye research] continues to take place in inadequate facilities. . . . The need for increased research space is one of the imperatives on which we have placed special emphasis. . . ."[2]

The FY 1980 appropriation for the NEI included $3 million for a construction grant program. These funds, which were made available until expended (that is, they could be awarded in a future fiscal year), were provided to increase the availability and to improve the quality of vision research facilities. In response to this Congressional initiative, the National Eye Institute conducted a preliminary survey in 1979 to determine the expected needs for facilities to conduct vision research. Department chairmen from 40 institutions listed proposed projects for a total estimated cost of between $65 and $72 million, with projected costs for individual projects ranging from $75,000 to $10 million.

Guidelines for the new program were made final in February 1980, but due to unforeseen delays beyond the NEI's control, applications were not solicited until the following September. Applications were developed, submitted, and reviewed over the next 18 months, and the first awards were made early in 1982.

The need for construction of clinical research facilities has been described by both professional and private groups interested in vision research. That need is further documented in this Plan. In each NEI program, needs and opportunities for research aimed at improving the diagnosis and treatment of eye diseases have been identified along with opportunities for research which may eventually lead to means of preventing such disorders. In particular, numerous opportunities for clinical research and clinical trials have been documented for such disorders as strabismus, amblyopia, retinal degenerations, corneal diseases, glaucoma, and cataract. The likelihood that such high priority clinical research will be initiated will be greatly enhanced by the availability of modern, well-equipped facilities with beds dedicated for research use.

The NAEC believes that construction of clinical research facilities is an important need for the vision research community. However, in a resolution passed in February 1982, the Council stated that the NEI's highest priority should continue to be the support of individual investigator-initiated research project grants. Additional funds for clinical research facilities should be considered only after resources are made available to support 60 percent of approved grants. The Council urgently requests private donors to assist in fulfilling this important need of the vision research community.

SPECIALIZED RESEARCH RESOURCES

Animal Breeding Colonies

The NEI should continue to provide for the maintenance and distribution of those animal models of human visual disorders which are of the greatest importance to vision research. The value and practicality of this approach have already been demonstrated by the successful completion of an NEI contract for the development and distribution of congenic strains of the Royal College of Surgeons rat which serves as an animal model of inherited retinal degenerations. Now, Irish setters and miniature poodles with inherited retinal degenerations are being bred and distributed to qualified investigators. The development of the canine model breeding project can be traced to a pilot feasibility study supported by the National Retinitis Pigmentosa Foundation. Where possible, fruitful interactions of this type between the NEI and organizations in the private sector should be encouraged.

Human Donor Eyes For Research

In recent years, some noteworthy progress has been made in obtaining human donor eyes for research purposes. Success has been limited, however, and has generally involved a single group of investiga-

tors working with a local eye bank or other private organization. The general unavailability of clinically characterized and optimally preserved donor eyes remains a major impediment to research advance. The registration of human donor eyes is best handled through eye banks and private foundations which have close contact with these patients. The NEI should thus continue to encourage the National Retinitis Pigmentosa Foundation, the Juvenile Diabetes Foundation, the Lions Eye Banks, and other interested organizations which have already began or are considering such donor programs on a national basis.

Communication among investigators and participating organizations should be encouraged and research protocols exchanged to ensure that donor eyes are obtained under conditions designed to preserve and distribute them for optimal use. The NEI should, through the use of the research project grant, continue to provide support for study of these eyes.

Consortium Grants

The Cooperative Cataract Research Group (CCRG) is a consortium of 22 research laboratories located throughout the United States which have pooled scarce material and personnel in a cooperative program of human cataract research. The success of the CCRG in fostering collaborative scientific studies on the normal and cataractous lens has been widely recognized. The NEI should encourage the CCRG to make full use of its potential for accelerating the pace of cataract research, particularly that of cataract epidemiology. As research needs warrant, other such groups may similarly join forces to pursue common goals.

RESEARCH CONTRACTS

The National Advisory Eye Council continues to endorse the NEI's selective and restricted use of the contract mechanism to fulfill certain program priorities or meet specific program needs. In general, contracts are used to support NEI-directed projects which may result in either enhanced research capabilities or improved prevention, diagnosis, and treatment of visual disorders. In contrast to the project grant system in which the research is conceived, designed, and initiated by the investigator, contract-supported projects are usually conceived and designed by the NEI staff, although in consultation with experts from outside the Institute. The NEI is responsible for maintaining control over contract specifications, methods, schedules, implementation, direction, and evaluation of the research or other work to be performed.

In practice, the NEI has used contracts primarily to support multicenter clinical trials (although other mechanisms such as research project grants can and do support such studies), to procure specialized research resources, or to support special initiatives, such as the World Health Organization Programme for the Prevention of Blindness.

In its 1978–1982 Plan, the Council noted that:

> The NEI considers the research contract the best way of supporting clinical research when all of the following apply: (a) the topic is one of considerable national importance; (b) NEI staff members and their advisors play a role in developing the concept and design of the study; (c) the performance of the study requires the collaboration of a number of institutions or clinics; and (d) the NEI has the staff resources to assume responsibility for the management as well as the sponsorship of the study.

In FY 1981 the NEI awarded $4.3 million to support 45 contracts, most of them ongoing. One of these provided close-out support for the Diabetic Retinopathy Study and 13 supported the multicenter Diabetic Retinopathy Vitrectomy Study. Twenty-three contracts, ten of which received funding in FY 1981, supported the multicenter Early Treatment Diabetic Retinopathy Study. In recognition of the importance of understanding the causes of cataract, the NEI is supporting a contract in which brunescent lenses are sent from India to the United States. This type of lens, which is scarce in the United States, is then distributed to qualified investigators by a committee of the Cooperative Cataract Research Group (CCRG) for biochemical and biophysical analyses. The NEI's role in the WHO Programme for the Prevention of Blindness is to support the gathering of epidemiological data on preventable or easily curable eye diseases in third world countries. The pilot Visual Acuity Impairment Study (see Chapter 1) accounted for five contracts. The remaining NEI contract supported a project to breed dogs with a hereditary retinal degeneration for the purposes of distributing the animals to qualified investigators.

In the future, the NEI should continue to use contracts in a similar manner. In general, research contracts should be used only for activities of the highest program priority, and then only when the steps required for attaining a desired objective can be specified in advance and in great detail.

INTRAMURAL RESEARCH

The development of the National Eye Institute's intramural program has followed the recommenda-

tions made by the forward-thinking group of ophthalmologists who spearheaded the drive for the development of a National Eye Institute, one of whom stated at the 1967 Congressional hearings to consider establishment of the NEI:

> As you gentlemen know, the National Institutes of Health have a research team at Bethesda unmatched by any in the world. The program at Bethesda centers around two principal areas: the first at the clinical center where the problems of disease are studied, and the second in the intramural laboratories which are devoted in the main to basic research.
>
> The establishment of an Eye Institute would provide the administrative mechanism for establishing research laboratories in blinding disease at Bethesda which could provide the model for research development as has been done in heart disease, cancer, neurologic disease, and arthritis and metabolism. [3]

These remarks showed foresight concerning the positive impact an NEI intramural program could have on the development of a national research program. For today, the small but vigorous NEI intramural program serves as a model for the integration of basic and clinical vision research and as a productive representative on the NIH campus of the important research being conducted in institutions across the country to alleviate eye diseases and blindness.

The NEI intramural program is valuable not only for its contributions to scientific knowledge, but also for several other reasons. The value to the NEI administration of having some of the top scientists in vision research on the staff is inestimable. They have been and continue to be of great assistance in helping the Director and other top NEI and NIH officials keep abreast of the latest scientific opportunities and achievements. Because these scientists maintain close relationships with their colleagues elsewhere in the vision research community, they also serve as an important channel of communication between the NEI leadership and vision scientists.

The National Eye Institute's intramural program is also an important national resource for vision research and research training. The clinical research facilities in the new NIH Ambulatory Care Research Facility will permit the NEI to place even more emphasis on direct clinical research training activities and the relationship of basic to clinical research. Also, mid-career and senior investigators from the vision research community will have more opportunities to spend sabbaticals at NIH and take advantage of the unique research opportunities and training facilities that exist in Bethesda.

The NEI intramural program is built upon a strong base of multidisciplinary research activity. Its program is focused on areas of research not extensively covered in the extramural vision research community, such as epidemiology and epidemiologic approaches to clinical research, immunology, combined laboratory and clinical approaches to neuro-ophthalmic problems, applications of basic clinical psychophysics, and, most recently, molecular biology. These initiatives closely follow the program priorities established in the 1977 National Vision Research Plan.

The National Advisory Eye Council believes therefore that the NEI intramural program should continue to be strongly supported. Further, it should continue to be monitored and evaluated project-by-project by the Board of Scientific Counselors, the formally chartered group of scientists from the extramural research community which reviews its progress. The Council would also like to be kept informed of the areas of research being investigated by NEI's intramural scientists as part of its ongoing assessment of the impact of the National Plan and the changes in research needs and opportunities that occur over time.

KNOWLEDGE TRANSFER AND INFORMATION DISSEMINATION

Fulfillment of the National Eye Institute's mission depends in great part on effective communication of the Institute's aims, policies, and programs, along with the results of research supported and conducted by the NEI. The NEI Office of Clinical Applications of Vision Research and the Office of Scientific Reporting are responsible for planning, coordinating, implementing, and evaluating NEI knowledge transfer, scientific reporting, press relations, and information dissemination activities.

In carrying out effective knowledge transfer and information programs, the NEI engages in the following activities:

- Monitoring progress in vision research.
- Identifying clinically applicable research results.
- Identifying emerging technologies and methods for diagnosis and treatment, fostering their evaluation, and making the results known to eye care specialists and primary health care providers.
- Supporting clinical trials to evaluate or compare treatments.
- Disseminating the results of clinical trials and other research by preparing printed and audiovisual information materials, including exhibits for public and professional audiences, by providing information to the media, and by disseminating public health education materials.

- Responding to public inquiries about eye diseases, disorders of vision, and vision research.
- Arranging special events such as press conferences, NIH consensus conferences, and tours.
- Working with professional societies to incorporate important research results into medical school and residency curricula.
- Collaborating with other Federal agencies, voluntary organizations, and professional societies to disseminate information on research results.

Need for Expansion of Knowledge Transfer and Information Programs

There are many reasons why the expansion of the NEI's knowledge transfer and information programs is necessary.

Among physicians, the transfer of new knowledge about clinically applicable research results is often slow. Communication of the Diabetic Retinopathy Study (DRS) results is a noteworthy example. Since 1976, when the NEI-supported study demonstrated that photocoagulation could save the vision of many people with advanced retinopathy, repeated efforts have been made to communicate the clinical significance of these results. The NEI and the DRS research group sent personal letters to every ophthalmologist in the country concerning the study's results, published scientific reports in numerous medical journals and medical news publications, held a press conference to communicate study results to the public, prepared scientific exhibits, and produced a film that documented study procedures which was widely shown at scientific meetings and in medical school ophthalmology departments. Yet, many people who could benefit from photocoagulation still go untreated, and some will go blind as a result. In 1979 a University of Michigan survey found that only 28 percent of family physicians and 46 percent of internists attending a medical education conference were familiar with the results of the DRS.[4] It is also evident from candidates taking ophthalmology board examinations that these important findings still are not given adequate emphasis in ophthalmology residency programs.

In spite of the placement of hundreds of articles on diabetic retinopathy in newspapers and magazines and numerous television and radio broadcasts, many diabetics and their families are still unaware of the potentially blinding complications of diabetes, of the existence of an effective treatment, and of the steps they can take to reduce the risk of visual impairment.

Furthermore, the need for more and better patient and professional education has been recognized by many organizations: the National Diabetes Advisory Board, the National Commission on Diabetes, virtually every state program affiliated with the Centers for Disease Control's Diabetes Control Program, the Indian Health Service, the National Diabetes Information Clearinghouse, the Diabetes Mellitus Coordinating Committee, the American Diabetes Association, the Juvenile Diabetes Foundation, and numerous hospitals and medical schools throughout the country.

There is a clear need for more information about other eye diseases as well. The National Eye Institute is just one of many organizations which together receive thousands of inquiries a month from people who want to know more about eye diseases and the latest advances in prevention and treatment. In many cases, people with treatable eye diseases and conditions are unaware that research has yielded an effective treatment, or they have so little information about a new therapeutic modality, they are reluctant to permit their physicians to employ it.

In summary, the NEI must communicate to health care providers and the general public knowledge of new ways to improve the prevention, diagnosis, and treatment of eye disease if the Institute is to ensure that the research advances it has supported are fully utilized. For this reason, knowledge transfer and information dissemination programs are essential to the fulfillment of the NEI's mission.

Recommended Future Activities

The NEI should expand its knowledge transfer and scientific reporting programs, placing special emphasis on the following projects:

- Monitoring progress in vision research to identify research results worthy of further dissemination to scientists, health care providers, the general public, and the media.
- Upgrading NEI information materials. Existing fact sheets and brochures should be reviewed, updated, and expanded as necessary. The need for additional printed and audiovisual information materials should be analyzed carefully, with special consideration given to the following topics: diabetic retinopathy, cataract, macular degeneration, glaucoma, retinitis pigmentosa, uveitis, visual impairment and its rehabilitation, aging-related eye disorders, eye disorders of childhood, and how to obtain additional needed information and services. Because of the expense of distributing printed materials, the NEI should try to develop alternative information distribution systems, perhaps enlisting the support of other government agencies, private organizations, professional societies, or industry.

- Disseminating information about NEI-supported clinical trials. Attempts should be made to increase both professional and public understanding of clinical trial methodology and the need for carefully controlled clinical trials. Information materials should be prepared and disseminated to the media. Efforts should be made to encourage patient recruitment for specific trials, when needed.
- Continue and expand the recently implemented diabetic retinopathy information campaign. The NEI should disseminate additional information on diabetic retinopathy to the print and broadcast media; contact reporters to describe the ocular complications of diabetes and the availability of a treatment that prevents many people from going blind; and solicit cooperation from other Federal agencies, voluntary organizations, and professional societies in this effort. In particular, the NEI should work with medical schools and professional societies to ensure that the results of the Diabetic Retinopathy Study are included in medical school curricula and in continuing medical education programs.
- Disseminating information about the NEI's program planning efforts. Communication is a vital aspect of implementing this National Plan. Following publication and widespread distribution of the Plan to the research community, government policy and decision makers, and public interest groups, further efforts should be made to increase awareness of NEI's program priorities and the potential contributions of vision research.

ROLE OF THE NEI IN INTERNATIONAL PREVENTION OF BLINDNESS

Today at least 40 million people in the world are blind, and in 20 years this number may double. Because eighty percent of this blindness could have been prevented with appropriate application of existing knowledge or could, even now, be cured, a major new international effort to reduce this toll is underway. The National Eye Institute is cooperating with several international agencies and organizations working to prevent and treat blindness by helping to establish and evaluate the research base related to this effort. Specifically, the NEI's activities are aimed at:

- Obtaining sound epidemiologic data on the prevalence of visual impairment and blindness due to all causes in various parts of the world;
- Evaluating available health technologies for blindness prevention and cure and promoting programs that are the most cost-effective and making these available to affected populations;
- Encouraging the controlled, clinical evaluation of findings from this research which appear to be promising; and
- Conducting and supporting vision research in various countries.

In carrying out these activities, the NEI:

1. Participates in formalized collaborative research and scientific exchange programs with Japan, India, and the U.S.S.R.
2. Collaborates with the World Health Organization's Programme for the Prevention of Blindness and, through its Bethesda intramural research program, serves as a WHO Collaborating Research and Training Centre for the Prevention of Blindness.
3. Participates in the National Institutes of Health Visiting Scientists Program.
4. Provides grant support for selected foreign investigators.

Recommended Future Activities

The NEI should continue a modest program of support for international activities that help to provide a knowledge base for worldwide prevention of blindness efforts, broaden the base of vision research, and bring about a better utilization of existing resources for vision research in participating countries. In addition, the NEI should serve as a catalyst to encourage support by other public and private agencies in the U.S. for the worldwide prevention of blindness.

NOTES

1. Personnel Needs and Training for Biomedical and Behavioral Research. Committee on a Study of National Needs for Biomedical and Behavioral Research Personnel, Commission on Human Resources, National Research Council. Washington, National Academy Press, 1981.
2. Department of Labor, Health and Human Services, Education, and Related Agencies Appropriations for Fiscal Year 1981, Part 4. U.S. Senate, Committee on Appropriations, 1980, p 128.
3. National Eye Institute. U.S. House of Representatives, Committee on Interstate and Foreign Commerce, Subcommittee on Public Health and Welfare, Serial 90–16, 1967, p 137.
4. Stross JK, Harlan WR: The dissemination of new medical information. *JAMA* 241:2622–2624, 1979.

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CROSS-CUTTING AREAS AND ISSUES

MANY OF THE RESEARCH projects the NEI supports deal with subjects or issues that cut across two or more of its five programs. Several of these topics have attracted considerable national interest and attention for scientific, economic, social, or political reasons.

Because of the importance of research in these areas, NEI periodically classifies, describes, and monitors its support for them. The Institute frequently is called upon by those at higher levels within the Executive Branch and by the Congress to report on the extent and nature of its support in several of these fields. The NEI is also an active participant on several trans-NIH committees, including the Diabetes Mellitus Coordinating Committee, the Nutrition Coordinating Committee, and the Committee on Research Related to Disease Prevention and Health Promotion.

The Council believes that it is important to analyze and track how the NEI's program relates to these broad subjects and to demonstrate the relevance of vision research to solving major problems of broad national interest. For this reason the Council recommends that the NEI continue to assess its activities that bear on the following topics:

- Prevention
- Diabetes
- Nutrition
- Aging
- Toxicology
- Genetics
- Immunology
- Epidemiology
- Neurobiology
- Molecular Biology
- Noninvasive Research and Diagnostic Techniques
- Refractive Errors
- Use of Animals in Vision Research

PREVENTION

The Department of Health and Human Services has embarked upon a campaign to give added emphasis to the importance of illness and injury prevention. *Healthy People*, the Surgeon General's Report on Health Promotion and Disease Prevention published in 1979, described a national prevention program for improving the health of the American people. Fifteen priority activities were identified including topics such as pregnancy and infant care, occupational safety and health, and infectious agent control. In 1980, a second report, *Promoting Health/ Preventing Disease*, identified specific and "measurable objectives" to be achieved by the year 1990 in each of the fifteen priority areas. The Secretary of Health and Human Services also called upon all NIH Institutes to identify and describe their ongoing research related to disease prevention and to give additional emphasis to this area.

The National Advisory Eye Council and the National Eye Institute welcome this DHHS prevention initiative. Since its establishment, NEI has made research that could lead to the prevention of eye disorders and diseases one of its primary goals. Currently, approximately one-third of the NEI budget supports research that is aimed at the ultimate prevention of eye disease or its sequelae: visual impairment, disability, and blindness. In FY 1981, the NEI supported 307 research projects

related to prevention at a total cost of $31,262,577. These have been categorized according to 12 prevention research initiatives. (See Tables 1 and 2.)

At present, few eye disorders can be prevented, and eye injuries take a significant toll despite the excellent school and industrial safety education programs of organizations such as the National Society to Prevent Blindness. However, through early diagnosis and treatment, it is often possible to prevent serious visual impairment or blindness.

In the Retinal and Choroidal Diseases program a major recent breakthrough has been the demonstration that appropriately timed laser treatment is highly effective in preventing or forestalling blindness from one form of aging-related macular dystrophy (senile macular degeneration) (see Chapter 2). However, more research is needed to find ways of preventing this disorder altogether. A number of investigators are also assessing the impact of early treatment of diabetic retinopathy in hope of being able to prevent progression of the disease to advanced stages that pose a high risk of blindness. Other NEI-supported studies are underway to understand better the relationship between oxygen therapy for premature infants and the development of retrolental fibroplasia (RLF), a major cause of infant blindness, and to evaluate the use of vitamin E to protect premature infants from this disease. The NEI is sponsoring a multicenter, controlled clinical trial to determine the effectiveness of laser treatment in preventing blindness from branch vein occlusion.

In recognition of the fact that infections and inflammations are a major cause of blindness in the world, NEI-supported studies in both the Retinal and Choroidal Diseases and Corneal Diseases programs are seeking to understand the immunologic basis of ocular inflammation. These include research on uveitis and studies aimed at understanding and controlling the factors which promote recurrence of ocular herpes simplex infections and at finding means of preventing trachoma infections. Other studies aim at preventing or controlling eye diseases related to nutritional deficiencies.

In the Cataract program, research is directed toward better understanding the effect of aging on the human lens and of finding means of preventing or arresting the formation of senile cataract. Investigators studying experimental diabetic cataract have described in detail how these opacities develop, including the role of the enzyme aldose reductase in their formation. Recently, the efficacy of aldose reductase inhibitors in preventing the formation of these cataracts in animals has been dramatically demonstrated. These findings of cataract researchers increasingly have implications in other areas of research as the relationship between aldose reductase and retinal vascular and neural complications in diabetes is unfolding.

In the Glaucoma program, research related to preventing visual loss from this disorder involves studies aimed at developing better means of early detection of elevated intraocular pressure, elucidating the mechanism of control of intraocular pressure, and more definitively describing fluid inflow and outflow in the eye.

In the Strabismus, Amblyopia, and Visual Processing program, studies have shown that impediments to normal visual input early in life, such as a congenital cataract or a misaligned eye, can have a profound impact on the development and function of visual centers in the brain and result in amblyopia. NEI-supported research currently pursued in this area includes studies of the critical periods in early visual development requiring normal visual input and the possibility of reversing the effects of early visual deprivation with drug treatment.

The National Advisory Eye Council strongly endorses the pursuit of research that will lead to prevention of eye disorders, injuries, and visual impairment. A review of the objectives of virtually every subprogram of this National Plan will show the research community's appreciation of the importance of prevention of eye and vision diseases and disorders. The Council believes that, although better and more effective means of diagnosing and treating disease must always be sought, the ultimate goal of biomedical research must be prevention of disease and disorders and the death, suffering, and diability they cause.

DIABETES

Diabetes, a disorder affecting an estimated 10 million Americans, can cause long-term, serious damage to virtually every tissue in the body, but it is particularly devastating to the tiny blood vessels of the nerves, kidneys, and eyes. For this reason diabetes is one of the main causes of loss of sight and visual impairment in the United States today. Diabetes affects a number of ocular tissues, but exerts its most harmful effects on the retina where it causes progressive breakdown of the normal vascular system, a condition called diabetic retinopathy. The resultant oxygen-starvation stimulates the growth of new abnormal blood vessels, which are fragile and may break and bleed into the center of the eye, thus impairing vision. Repeated hemorrhages from these vessels may be accompanied by the formation of scar tissue, which pulls on the retina and in many cases leads to irreversible retinal detachment and blindness.

TABLE 1. National Eye Institute Support for Prevention-Related Research, FY 1981

Prevention Initiative	No. of Projects	Amount
Prevention of hereditary and developmental degenerations of the retina	31.5	$3,308,039
Prevention of proliferative diabetic retinopathy, retrolental fibroplasia, and other proliferative retinopathies	55.0	7,127,889
Prevention of blindness from branch vein occlusion	7.0	639,117
Immune mechanisms underlying uveitis and other ocular inflammations	42.0	4,282,754
Investigation of the effects of drugs, light and environmental factors on the retina and lens	16.0	1,384,047
Prevention of recurrent corneal infection from herpes simplex virus	18.5	1,921,107
Prevention of trachoma	5.5	679,982
Basic research related to the prevention of human senile cataract	16.5	1,485,318
Prevention of diabetic cataract	13.5	1,327,093
Prevention of glaucoma	30.0	2,959,921
Research on the effects of visual deprivation related to the prevention of amblyopia and strabismus	50.0	4,154,447
Prevention and/or control of eye diseases related to nutritional deficiencies	10.0	1,036,013
Prevention of visual impairment from corneal burns and ulcers	7.5	647,349
Prevention of nearsightedness and other refractive errors	3.0	309,501
Population studies to identify eye disease risk factors	1.0	($31,263)*
Total	**307.0**	**$31,262,577**

*The funding for these population studies is included in eight prevention initiatives in which risk factors are being assessed.

TABLE 2. National Eye Institute Support of Prevention-Related Research by Program and Mechanism, FY 1981

NEI Program	Grants		Contracts		Intramural		Total	
	No.	Dollars	No.	Dollars	No.	Dollars	No.	Dollars
Retinal and Choroidal Diseases	84	$8,107,605	24	$3,497,000	17	$2,464,388	125	$14,068,993
Corneal Diseases	60	5,753,828	—	—	2	289,928	62	6,043,756
Cataract	36	3,184,518	—	—	3	434,892	39	3,619,410
Glaucoma	25	2,048,517	—	—	6	869,784	31	2,918,301
Strabismus, Amblyopia, and Visual Processing	49	4,132,117	—	—	—	—	49	4,132,117
Other*	—	—	1	480,000	—	—	1	480,000
Total	**254**	**$23,226,585**	**25**	**$3,977,000**	**28**	**$4,058,992**	**307**	**$31,262,577**

* Support for the nationwide Visual Acuity Impairment Survey which includes the identification of possible risk factors as one of its goals.

From its inception, the National Eye Institute has recognized the importance of diabetes as a leading cause of visual impairment and blindness and has placed great emphasis on basic and clinical research in this field. In fact, soon after its establishment, the NEI launched a major clinical trial to evaluate argon laser and xenon arc photocoagulation in the treatment of diabetic retinopathy. When the trial began, photocoagulation had been in use for more than a decade, yet no definitive study had been made of its safety and efficacy. The nationwide Diabetic Retinopathy Study involved sixteen clinics and over 1700 patients in what was the largest controlled clinical study in the history of eye research. In 1976, the study's first results were published, providing dramatic evidence that photocoagulation could reduce the risk of severe visual loss from diabetic retinopathy by more than half. Later reports confirmed the treatment's efficacy in eyes with moderate to severe retinopathy and identified characteristics of the disease which, if present alone or in combination, increased the risk of blindness in an eye. These findings have given ophthalmologists reliable data on which to base decisions about the management of their diabetic patients.

The DRS did not, however, provide data to indicate whether photocoagulation treatment at earlier stages of diabetic retinopathy could slow the disease's progression to advanced stages, where sight is most threatened. Accordingly, the NEI began the Early Treatment Diabetic Retinopathy Study in 1980 to test this hypothesis and also to evaluate the possible role of aspirin, alone or in combination with photocoagulation, in treating this disease. This study, which is continuing, involves 23 clinical centers throughout the United States. About 3200 patients are expected to be enrolled, and the trial is planned to last a total of five to seven years.

Another clinical trial was begun in 1976 to evaluate vitrectomy, a procedure designed to restore vision lost after severe hemorrhaging into the eye resulting from diabetic retinopathy. In vitrectomy, the eye surgeon inserts a thin hollow needle with a rotating blade into the eye. As the blade rotates at hundreds of revolutions per second, the blood-filled vitreous and scar tissue are simultaneously cut and sucked out of the eye through the hollow needle. The key question addressed in the 12-clinic Diabetic Retinopathy Vitrectomy Study is what is the best timing for this treatment.

While these clinical trials continue, the NEI supports a wide range of basic research related to the ocular effects of diabetes. The NEI is the primary source of funding for such research and the findings from these studies bear not only upon diabetic eye disease but upon systemic diabetes as well. Improved methods of measuring retinal blood flow developed through this research have shown that the blood flow rate in the retinal vessels of diabetics differs from that of non-diabetics. The techniques of fluorescein angiography and vitreous fluorophotometry, which involve following the passage of an injected fluorescent dye through ocular tissues, have provided important research and diagnostic information about the leakage of minute amounts of blood from damaged retinal vessels. Use of these methods promises earlier diagnosis of diabetic retinopathy, hence earlier treatment, and improved prevention of visual impairment from this disease.

Diabetics may also have serious eye problems resulting from their disease other than those associated with retinopathy, for example, cataract and glaucoma. New evidence confirms that diabetics develop cataracts at an earlier age than non-diabetics. Although the "pure" diabetic cataract that occurs in animals with diabetes may not occur in humans, diabetes may hasten the onset of senile cataracts. Laboratory research on diabetic cataract has resulted in the identification of an enzyme, aldose reductase, that triggers lens opacities in animals in the presence of high levels of sugar. Recent evidence suggests that this enzyme is also present in other tissues and may be at the root of diabetic complications in the retina, peripheral nerves, and kidney. Several chemical aldose reductase inhibitors have been developed and are in various stages of clinical testing. One clinical study has already provided evidence that an aldose reductase inhibitor has a beneficial effect in restoring motor nerve function in diabetics with peripheral neural impairment.

The National Eye Institute has become a leader among organizations and agencies concerned with diabetes. The NEI Director serves as a member of the National Diabetes Advisory Board created by Public Law 94-562, the Arthritis, Diabetes, and Digestive Diseases Amendments of 1976. The NEI is also represented on the Interagency Diabetes Mellitus Coordinating Committee, which includes delegates from every Federal agency involved in diabetes reserach. An NEI staff member also serves on the Trans-NIH Diabetes Mellitus Coordinating Committee. In 1981, a member of the NEI staff chaired the planning committee for an NIH work-

shop to evaluate animal models for diabetes research, the results of which have been published.[1] Finally, the NEI is represented on the Juvenile Diabetes Foundation's Scientific Advisory Committee for the National Diabetes Research Interchange. This committee is dedicated to the procurement, preservation, and distribution of human tissues and organs for diabetes research.

The NEI has also provided leadership in disseminating information on the findings from ocular diabetes research. A professional and public information campaign has been launched to alert various target groups to the importance of proper attention to and care of the eye problems of diabetics. The Institute published a booklet "Diabetes and Your Eyes" last year, which is being widely distributed to diabetic patients and their families, health professionals, and others interested in this subject. Dissemination of this publication is a cooperative effort between the NEI and the National Diabetes Information Clearinghouse administered by NIH's National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases; DHHS's Centers for Disease Control; and the Juvenile Diabetes Foundation.

In FY 1981 the NEI supported 155 research projects that were related to diabetes at a total cost of $16.7 million. Opportunities and priorities for future research in this field are highlighted in the reports of the Retinal and Choroidal Diseases and Cataract programs. These are summarized in Chapter 2 of this volume and appear in full in *Volume Two*, Parts One and Three, of this Plan.

NUTRITION

Adequate nutrition is a major goal of many health promotion and disease prevention programs and is especially important for normal human growth and development. In the past decade there has been increasing public interest in the relationship between nutrition and health, particularly in food contents and safety and the link between diet and disease.

Although nutritional deficiencies are not a major cause of eye problems in the United States or Europe, malnutrition, particularly vitamin A deficiency, is a leading cause of childhood blindness in developing nations throughout the world. However, there are nutrition-related eye problems even in developed countries, including the complicating side effects of some prescribed medications, which interfere with normal vitamin metabolism, and several inherited or aquired diseases, which interfere with the absorption and/or metabolism of individual vitamins.

Federal support of nutrition research is decentralized, but the Department of Health and Human Services (primarily through NIH) and the Department of Agriculture together account for over 90 percent of this effort. In the Food and Agriculture Act of 1977, Congress called for better coordination among DHHS, USDA, and other Federal organizations in nutrition research. Since then, considerable progress has been made in coordinating Federal nutrition research. The White House's Office of Science and Technology Policy has established a Joint Subcommittee on Human Nutrition Research with representatives from USDA, DHHS, and seven other departments and agencies. Within DHHS, a Nutrition Coordinating Committee has been organized and NIH has established its own Committee to coordinate the nutrition research and training activities of the various Institutes.

One of the accomplishments of the NIH Nutrition Coordinating Committee has been to establish a computerized inventory of NIH-sponsored nutrition projects. As a contributor to this data base, NEI has attempted to define its program interests in nutrition and to identify specific grants and intramural projects in this field.

Many NEI-supported projects are exploring the normal metabolism of ocular tissues, particularly the role of vitamin A and other nutrients in normal retinal and corneal function. The effects of experimental malnutrition are also being studied with particular emphasis on deficiences of proteins, amino acids, and certain vitamins. One important area of investigation is the identification of possible nutritional risk factors for the development of cataract. Other studies are exploring the effect of individual nutrients on the metabolic processes involved in immune responses. Research indicates that a wide range of optic nerve disorders may be caused by nutritional deficiencies. A specific enzyme defect has been identified as the cause of a rare form of inherited retinal degeneration, gyrate atrophy, and a diet has been designed which is aimed at reversing the visual effects of this disorder.

As part of its responsibility to assist in the worldwide effort to prevent blindness, the NEI has taken advantage of a unique opportunity to study xerophthalmia and keratomalacia, two corneal disorders that result from prolonged vitamin A and protein deficiency. Keratomalacia is particularly tragic because it strikes children between the ages of one and six years. In Asia alone it afflicts at least 100,000 children each year. Worldwide, an estimated one of every 500 children between ages one and six are affected. The NEI is collaborating with the National Institute of Nutrition in Hyderabad, India, in operating a clinical research center for nutritional blindness supported by Public Law 480 funds.[2] One major goal of the center is to define more clearly the factors, in addition to vitamin A deficiency, that increase a child's risk of nutritional blindness, and to

evaluate the efficacy of various forms of dietary supplementation.

In FY 1981, the NEI supported 81 research projects related to nutrition, at a total cost of $4.3 million.

AGING

A great many diseases and disorders of the eye are associated with aging. As a result of advances made in other medical fields, people today are living longer and are healthier, yet many are kept from fully enjoying the benefits of their longevity by visual problems. Statistics from the Department of Commerce indicate that in just fifty years the number of people aged 55 and older will constitute almost a third of the U.S. population. Improved prevention, diagnosis, and treatment of eye diseases and disorders of the elderly are therefore of great importance.

Nearly one-third of all visits to physicians' offices for medical eye care in the United States—over 9 million visits a year—are made by individuals 65 years of age and older. More than half of all visual impairment occurs in people age 65 or older and more than 266,000 people over age 65 are legally blind. This is compounded by the addition of more than 25,000 new cases of legal blindness each year among those age 65 and over.

Increasing national concern for vision problems of the elderly led recently to the convening of two White House conferences. The first was a "mini" White House Conference on Vision and Aging, held in January 1981 at the request of the White House Conference on Aging by the American Foundation for the Blind and 15 co-sponsors. Participants in this conference generated a preliminary list of recommendations for the White House Conference on Aging held in November/December 1981. These recommendations were made in six areas: public education, rehabilitation and treatment, low vision and public policy, professional education and professions, research, and financing and legislation.

Retinal and Choroidal Diseases

This National Plan identifies research needs and priorities for diseases and disorders whose incidence increases markedly with age. In the Retinal and Choroidal Diseases program, studies of aging-related maculopathy (senile macular degeneration), retinal detachment, and the aging of visual cells have been highlighted. Because little is known about the cause of macular disease, the Retinal and Choroidal Diseases Panel has established as a research objective obtaining more information about the causes of this disease by pursuing specific biochemical, histologic, and metabolic studies. Because aging of the photoreceptors, the light sensitive rod and cone cells of the retina, is thought to be a major factor in macular disease, another research objective of the Retinal and Choroidal Diseases program is to develop methods to prevent or slow photoreceptor aging in humans. There is also need for case-control studies of patients with aging-related maculopathy and of age-, race-, and sex-matched control patients without the disorder. Although effective means of preventing macular disease have not yet been found, argon laser photocoagulation has been shown of great value in preserving vision in patients with certain types of the disease.

The vitreous humor which fills the center of the eye is normally in a gel state, but with age the gel shrinks and becomes partly liquified. When the vitreous shrinks, it may pull on the retina and create a retinal break. The fluid component of the vitreous can pass through the retinal tear, accumulate behind the retina, and cause a retinal detachment. Thus, another objective of the NEI Retinal and Choroidal Diseases program is to study the development, structure, metabolism, function, and immunologic properties of the normal vitreous and how these are altered in aging and disease.

Corneal Diseases

The tear film on the surface of the eye is in direct contact with the environment. It protects the eye from injury and disease, and maintains the health of the underlying cornea and conjunctiva. Because abnormalities in the tear film often occur with aging, a research objective of the NEI Corneal Diseases program is to achieve better understanding of the normal tear film and the changes in it that occur with aging and disease. Corneal dystrophies, a term for a variety of relatively uncommon but troublesome degenerative disorders, are usually inherited but may also be aging-related.

Cataract

Because the most prevalent human cataract is clearly related to aging, there is a real need to understand the aging process in the lens. Evidence indicates that practically everyone will acquire cataracts if he or she lives long enough, but the age of onset varies greatly among individuals. Aging-related lens changes are present in 42 percent of people age 52–64 years, 73 percent of those age 65–74 years, and 91 percent in those 75–85 years of age.

The National Eye Institute Cataract program has as one of its research objectives gaining a better understanding of the basic properties of the normal lens and the effects of aging on lens structure and

function. A need has been identified in this National Plan for additional studies using many different approaches—physiological, physiochemical, morphological, cell biological, and biochemical—to determine the basis of cataract formation and aging in man.

Despite its prevalence, little is known about the natural history of the aging-related cataract. Some progress has been made, however, in identifying possible risk factors for its development, including environmental and genetic factors and those secondary to other diseases. For example, there are indications that diabetes can hasten cataract development. The Council recognizes the importance of research in this area and has recommended as other research objectives in the Cataract program determining the cause(s) and pathogenesis of aging-related cataract including its risk factors and seeking the means to prevent, delay the progress of, or reverse the cataractous process. At present, cataracts can be treated only by surgery, which may be indicated when there is a visual impairment that interferes with an individual's daily life. Cataract extraction, followed by successful fitting of a substitute artificial lens, is a successful means of restoring useful vision in 90 to 95 percent of cases.

Glaucoma

The most common types of glaucoma mainly affect older people, with an increasing prevalence with each decade above age 40. The prevalence of ocular hypertension rises from approximately 2 percent at ages less than 40 years to 9 percent at ages greater than 70, although the exact relationship between this rise in intraocular pressure and visual loss from glaucoma is not well understood. The proportion of those individuals with elevated intraocular pressure who have vision loss rises from about 2 percent at age 40–49 to about 30 percent for those over age 70. This dramatic rise in the proportion of those with damage to the optic nerve and loss of vision seems to indicate a greater susceptibility of the optic nerve to damage in the elderly, the cause of which is unknown at this time.

The prevalence of the most common type of glaucoma, primary open-angle, rises from 0.02 percent for those 40–49 to 2–3 percent for those over age 70. Early detection and treatment before visual function is affected are vital. In the NEI Glaucoma program the Plan identifies as a research priority understanding the fluid outflow system in normal, aged, and glaucomatous eyes. Also, angle-closure glaucoma, which is due to a gross physical obstruction of fluid outflow from the eye, typically occurs in older people; this is also an area identified as needing additional research.

Strabismus, Amblyopia, and Visual Processing

Presbyopia, which is the gradual loss of ability to change the focus of the eye from one viewing distance to another, usually begins in individuals in their early to mid 40s. Statistics indicate that at least 90 percent of people over age 45 must wear corrective lenses at least part-time to see nearby objects or read fine print; this is primarily due to presbyopia. Although presbyopia is easily corrected by reading glasses or bifocal lenses, the cause of changes in refraction which occur with aging is not understood at this time. In the Strabismus, Amblyopia, and Visual Processing program, the Plan stresses the need for research to understand the changes which lead to refractive errors, particularly the aging-related changes in the lens and ciliary body that lead to presbyopia, in an effort to find means of treating or ways of preventing them.

Visual Impairment and Its Rehabilitation

In recognition of the special problems associated with visual impairment and its rehabilitation, the National Advisory Eye Council formed a sixth program planning Panel to assess research needs and opportunities in this field. Visual impairment and legal blindness are most common among the older adult population and their chief causes are conditions associated with aging. Serious visual problems can limit the independence of elderly people in society, increase their susceptibility to falls and other injuries, and lessen the enjoyment of life that seeing provides. In recognition of the great personal toll on afflicted individuals and their families as well as the socioeconomic impact of visual impairment, the Panel identified as a priority the study of the special problems and adaptations required in response to visual impairment in the older population.

The National Advisory Eye Council believes there must be a substantial improvement in knowledge of the visually impaired population to define better its demographic and etiologic characteristics and to improve rehabilitation programs.

To obtain maximal use of their residual vision, some older persons, particularly those with degenerative diseases of the macula and optic nerve, may require low vision aids. These aids may be prescribed in the form of glasses, mounted so they can be hand-held, or rested on reading material. Some electronic aids are quite remarkable—and expensive. Many affected individuals believe that such sophisticated aids are worth their price, but often just the addition of simple magnification makes life much more comfortable for a visually impaired person. The NEI and the Council consider the scientific

evaluation of various types of visual aids a research priority. Some projects that aim to enhance the mobility of visually impaired persons are relevant both to totally blind individuals and partially sighted persons.

In Fiscal Year 1981 the NEI supported an estimated 94 projects directly concerned with problems relating to the aging eye, at a total cost of $6,578,000.

TOXICOLOGY

Over the past several decades numerous new chemicals have been introduced into the environment. Nearly 48,000 chemicals are used industrially in the United States and there are 5,500 food additives and 4,000 medicinal drugs. Americans are exposed to at least 1,200 compounds found in household products. Although only a small number of these substances are known to be highly toxic, little is known about the short- and long-term health effects of many commonly used chemicals and drugs. The National Eye Institute provides annual data for the Department of Health and Human Services' National Toxicology Program (NTP) on research it supports related to toxicology. The NTP coordinates those Department programs aimed at developing the scientific information necessary to protect the health of the American people from exposure to hazardous chemicals.

It is known that many drugs and chemicals can damage the eye, often seriously and irreversibly. The retina is particularly susceptible to such agents because it has special nutritional requirements, and because it functions in a rigorously controlled environment that has an exceptionally narrow tolerance for change. There is abundant evidence that drugs that do little or no harm elsewhere in the body can damage the retina.

The cornea, lens, aqeuous outflow channels, and optic nerve are also especially vulnerable to toxic insult. The NEI supports studies of adverse effects of ophthalmic drugs and drug vehicles on the corneal epithelium. Many drugs and chemicals applied to the eye or taken systemically, for example, corticosteroids, can cause cataract. The latter also can cause glaucoma to develop in susceptible individuals. Antiglaucoma medications are also being evaluated for therapeutic use in lowering intraocular pressure with the lowest toxic side effects.

Although the hazards to the eye posed by certain chemicals are well-known, the effects of many others are either less well understood or unknown altogether. The study of ocular toxicology is relatively new and underdeveloped and as yet has not attracted a sufficient number of investigators. Although in the course of drug development, ocular toxicity receives more attention today than it did ten years ago this effort is still inadequate. Especially in the development of systemic drugs not intended for the treatment of eye disease, pharmaceutical companies and testing laboratories usually lack the inhouse expertise in ocular physiology and pathology necessary for proper evaluation of ocular toxicity. And, even with adequate screening for acute ocular toxicity, drugs whose effects on the eye are subtle or slow to develop may reach the market. Even eye specialists may not recognize these early effects because they are revealed only by special tests which are not routinely performed in the physician's office.

In FY 1981, the NEI supported 10 toxicology-related research projects at a total cost of approximately $846,000. These projects included studies of the toxicity of antiviral drugs in the treatment of herpes simplex virus; the toxic side effects of several classes of antiglaucoma drugs, including safety and efficacy studies on timolol; the relationship between topically applied drugs and drug-induced edema after intraocular surgery; and the relationship between the use of steroids in treating inflammatory diseases and the development of toxic side effects, including glaucoma and cataract.

Given the potential hazard and the considerable gaps in knowledge in this field, an expanded effort in basic and clinical ocular toxicology is clearly warranted. Specific discussions of research needs and opportunities in ocular toxicity may be found in the following sections of Volume Two of the National Plan: Part One: *Retinal and Choroidal Diseases*, Chapter 7, "Toxic, Nutritional, and Environmental Disorders;" Part Two: *Corneal Diseases*, Chapter 2, Part 3: "Drug Delivery and Toxicity;" Part Three: *Cataract*, Chapter 6, "Cataract Induced by Environmental and Toxic Effects;" and Part Four: *Glaucoma*, Chapter 1, "Etiology, Epidemiology, Management, and Therapy."

GENETICS

Of the approximately 2,000 known human genetics disorders, an estimated 30 percent affect the eye. Hereditary and congenital diseases are the cause of blindness in one of every five blind people in the country—almost 100,000 Americans—and an additional 300,000 suffer from visual impairment from these causes. Because such visual impairment often begins in early life, the economic, social, and personal costs are substantial. The National Eye Institute therefore emphasizes research aimed at

early diagnosis, effective treatment, and ultimate prevention of hereditary and congenital diseases.

The science of genetics is broad and diversified, focusing on how hereditary information is transmitted and translated into various characteristics. NEI-supported studies include those of the basic mechanisms of inheritance and human genetic diseases. As more is learned about the nature of genetics and the inheritance of genetic disorders, it may be possible to limit the incidence and impact of these conditions. Families at high risk of having affected children can be identified and genetic counseling offered.

Retinitis pigmentosa, the most common of all inherited retinal disorders, affects between 50,000 and 100,000 people in the United States alone, and its cause is unknown at this time. Knowledge has increased substantially in the last 5 to 10 years as the result of basic research on the normal retina and pigment epithelium, the development of noninvasive techniques to study affected individuals, and the delineation of specific biochemical defects in animal models. The genetic factors have been difficult to unravel, but early diagnosis is helpful in establishing hereditary patterns in some families and identifying those families at high risk for having more affected children.

Substantial progress has been made in understanding gyrate atrophy of the retina and choroid, based on a sequence of investigations which has progressed from research in the laboratory to improved patient care: the detection of elevated levels of the amino acid ornithine in blood and urine of patients with this disease, the determination that high levels of ornithine are toxic to retinal pigment epithelium, the delineation of the defect responsible for the elevated ornithine, and the development of a special diet to reduce plasma ornithine. Studies of this disorder continue.

Corneal dystrophies include a heterogeneous group of inherited disorders that may begin early in life or may become manifest with aging, such as Fuchs' dystrophy or keratoconus. Macular corneal dystrophy (MCD) is the most thoroughly studied of all the inherited disorders of the cornea. MCD involves a gradual accumulation of opacities which are whitish in color, usually begin during adolescence, and accumulate within the stroma, the middle layer of the cornea. Corneal grafting is the only method of treatment currently available. NEI-supported research has been seeking to determine the nature of the material that is stored in this disease, but the basic metabolic defect in this inborn error of metabolism is still not known.

The exact causes of many corneal dystrophies are unknown at this time, but prevalence varies with geographical location and the frequency of the responsible gene in the population. Macular corneal dystrophy, for example, is rare in many parts of the world, but there are some inbred, isolated communities, such as those in the Appalachian mountains, which have a greater frequency of this disorder than those in other regions.

Genetic cataracts can occur at birth or appear at a later stage in development as infantile or juvenile cataracts. A strong genetic influence has been observed in presenile cataracts and senile cataracts often run in families. The natural histories of human genetic cataracts are not often described, and little research is being done on them, but several animal strains with genetic cataract have been utilized for detailed genetic and molecular biological studies on cataract development. Four different mouse models are being used in NEI-supported research, and a large body of genetic information now exists on them so that linkage maps can be made between cataract and other genetic loci. Dog and rat models of genetic cataracts are currently being developed in research laboratories funded by the National Eye Institute.

In FY 1981 the NEI supported 146 grants for genetic research at a total cost of $12.7 million.

For further discussion of NEI supported research in genetics, see Volume Two of the National Plan: Part One: *Retinal and Choroidal Diseases*, Chapter 4, "Developmental and Hereditary Disorders;" Part Two: *Corneal Diseases*, Chapter 4, "Corneal Edema, Endothelial Dysfunction, Dystrophies, and Inherited Diseases;" and Part Three: *Cataract*, Chapter 5, "Nongenetic Congenital and Genetic Cataracts and Dislocated Lenses."

IMMUNOLOGY

One of the most important and productive areas of biomedical research today is the field of immunology. The last few years have seen major advances and the development of many new concepts and discoveries about how the body responds to infection. Particularly exciting discoveries have been made in research on the molecular basis of how the body responds to foreign substances, including the nature of autoimmune diseases that are caused by the body's abnormal response to its own tissue.

Ocular infection can be caused by a diverse array of infecting organisms; the special environment of the eye provides unusual opportunities for these organisms to proliferate and destroy tissue. Certain ocular structures, such as the cornea, lens, and vitreous, do not normally have blood vessels, and this alters their immune response to foreign substances, whether desirable, such as transplanted tissue, or undesirable, such as infecting viruses, bacteria, or fungi. Abnormal functioning of the immune system may be an important factor in the

development and spread of eye cancers, including retinoblastoma.

Many infecting agents can become latent and lie dormant in tissues of the body for weeks, months, or years before expressing their infective nature. In this dormant state, the viruses cannot be eradicated by any medications now available. For example, herpes simplex viruses can become dormant in nerve tissue behind the eye and then be stimulated to become active again, often in response to some physical stress, such as a fever or other illness.

About 10 percent of all visual impairment in the United States is caused by uveitis, which is an inflammation of the inner eye. National Eye Institute intramural scientists have discovered that many cases of uveitis are autoimmune in origin and have identified specific retinal and lens antigens that are capable of inducing these conditions. Most recently, the NEI investigators have demonstrated that the autoimmune reaction in uveitis can be stopped and vision saved with a new drug, Cyclosporine, first used to suppress rejection of transplanted kidneys. This drug, which has already been tested against ocular inflammation in animals and is currently being tested in humans, shows promise as a powerful weapon against uveitis. NEI-supported researchers are testing various other anti-inflammatory agents for their safety and efficacy against ocular infections and inflammations. These include antiviral agents, various steroid compounds, and interferon.

A major breakthrough in immunology is the ability to utilize monoclonal antibodies. These antibodies are produced by hybridomas, which are hybrids between a leukemia cell and a spleen cell (see section on Molecular Biology). The hybridomas can be grown in culture, where they form almost unlimited quantities of a single type of antibody that can bind to specific structural features of cells. These monoclonal antibodies can be used as a very specific biological probe to detect changes in cell characteristics that occur during development. They also promise to be useful for monitoring the changes that occur during the progress of a pathological condition or during recovery.

The National Eye Institute is also supporting research on the genetics of the immune response. Some animal species are more resistant to certain infections than others, and the basis for this resistance is being explored in inbred strains of mice to determine how inheritance affects the behavior of the immune system. Similarly, some strains of animals are more susceptible than others to autoimmune diseases, and the genetic and molecular basis for this increased susceptibility also is being explored.

In its last program planning report, *Vision Research—A National Plan: 1978–1982*, the National Advisory Eye Council identified a number of research areas in immunology that needed to be expanded. These areas included the immunological aspects of ocular diseases and the application of newer concepts and methodologies in immunology to the study of the visual system. It was recognized that research in immunology of the visual system could benefit from an infusion of new ideas provided by immunology research outside the vision field. For this reason, in 1979–1980 the National Eye Institute organized a series of workshops to encourage communication between vision scientists and those in immunology research.[3–5] The workshops were successful in stimulating a fruitful interaction between clinicians and basic scientists, and several collaborative research efforts have begun as a result.

Just as the publication of the last National Plan served to stimulate research interest in ocular immunology, the National Advisory Eye Council and the National Eye Institute hope that this latest Plan will help expand interest in new and promising areas in this field. Research needs and opportunities in ocular immunology have been identified in various sections of Volume Two including Part One, *Report of the Retinal and Choroidal Diseases Panel*, Chapter 2, "Inflammatory Disorders," and Part Two, *Report of the Corneal Diseases Panel*, Chapter 1, "External Ocular Infections and Inflammatory Diseases," Chapter 2, "Ocular Surface Problems," and Chapter 5, "Corneal Transplantation and Wound Healing."

EPIDEMIOLOGY

Epidemiology is a quantitative discipline concerned with both the distribution and determinants of disease in the population. As such, it provides a broad perspective of the patterns of disease occurrence, identifies the factors associated with its development, and tests etiologic hypotheses. Because knowledge of etiologic factors may lead to preventive measures, epidemiology is considered to be the basic science of preventive medicine.

Epidemiologic research has made remarkable contributions to the prevention and control of infectious diseases and to understanding the natural history of chronic conditions, such as cardiovascular diseases and cancer. In contrast, this productive approach has until recently seldom been used to study noninfectious eye disorders and vision problems.

Epidemiologic studies of disease have descriptive, analytic, and experimental aspects. Through these three approaches, epidemiology aims to obtain information to measure the magnitude of disease, determine its risk factors, and improve patient outcome.

Descriptive epidemiology is concerned with measuring the numbers of persons affected by a disease and describing their characteristics. Descriptive studies are directed to 1) measuring the overall rates of disease occurrence in the population; 2) determining the distribution of disease in different population subgroups according to age, sex, ethnic groups, and other demographic variables; 3) monitoring disease trends; and 4) analyzing geographic patterns of disease occurrence, such as variations in disease rates between countries, states, or urban and rural areas.

A major role for descriptive studies is to obtain comprehensive information on the natural history of the disease in the population. The only survey to date specifically designed to determine the distribution of major eye diseases in a defined population is the Framingham Eye Study, which measured the prevalence of cataracts, aging-related macular dystrophy (senile macular degeneration), open-angle glaucoma, and diabetic retinopathy in a population aged 52 to 85. In addition to providing needed information on the frequency and distribution of these diseases, this NEI-supported study has served as a basis for further research into these leading causes of visual loss. Descriptive epidemiologic data on most eye conditions, however, are still unavailable.

Analytic epidemiology is directed to the identification of environmental and genetic factors that influence the risk of developing disease. Analytic epidemiologic studies test etiologic hypotheses which have been generated by clinicians, basic scientists, or epidemiologists. Although few studies of this type have investigated eye problems, those that have made important contributions, such as the identification of oxygen administration as the cause of retrolental fibroplasia in premature infants, the establishment of an association between cataract and diabetes, and the identification of systemic hypertension as an aggravating factor in diabetic retinopathy.

Experimental epidemiology refers to the evaluation of preventive, diagnostic, and therapeutic measures. This evaluation is implemented through carefully planned clinical trials, which are designed in collaboration with clinicians and statisticians. The nationwide Diabetic Retinopathy Study, a large, multicenter clinical trial, demonstrated that visual impairment from the proliferative form of diabetic retinopathy can be sharply reduced by extensive retinal photocoagulation. This trial was so successful that additional collaborative clinical trials in diabetic retinopathy, aging-related maculopathy, branch vein occlusion, and sickle cell retinopathy have been initiated.

Because epidemiology has the potential for making significant contributions to vision research, the application of each type of epidemiologic methodology to eye and vision problems needs further development. The incidence and prevalence of visual impairment and its causes in the general population need to be determined. Another high priority is the implementation of epidemiologic case-control studies to identify risk factors for major causes of visual loss, such as aging-related maculopathy, cataracts, glaucoma, and diabetic retinopathy. Such studies can evaluate the role of likely etiologic factors and delineate groups at high risk of disease. Continuing involvement of epidemiologists in clinical trials is necessary to evaluate rigorously the safety and efficacy of preventive and treatment methods. Another important priority is the training of investigators in the epidemiology of eye diseases and vision disorders.

NEUROBIOLOGY

In *Science and Technology: A Five-Year Outlook*, the National Academy of Sciences, predicted that by the 21st century, neuroscience may well be the dominant science.[6] Certainly, extraordinary progress has been made in the past few decades in understanding how the nervous system mediates all our behavior—from the level of single molecules, to functional aggregates of neurons, to entire integrative systems that underlie our conscious experience of the world and our responses to it. NEI-supported vision researchers have been at the forefront of this revolution in understanding our biological natures, frequently working in interdisciplinary teams representing such previously disparate disciplines as biology, chemistry, psychology, biophysics, mathematics, engineering, ophthalmology, physiological optics, and neurology.

In 1981 the Nobel Prize for Physiology or Medicine was shared by two long-time NEI grantees, David Hubel and Torsten Wiesel, and Roger Sperry, a grantee of the National Institute of Mental Health, for their work in neurobiology. Hubel and Wiesel's award was for their studies of the structure and function of the central visual pathways and how their development can be modified by the particular visual experience of the infant. Their work has had enormous influence on general conceptions of how elements in the brain selectively respond to stimuli and of the plasticity of the nervous system in general. These insights can have tremendous practical significance in the prevention and treatment of visual sensory disorders such as amblyopia (lazy eye).

Current investigations are developing powerful new techniques which will allow the microdissection of the visual neurons, to identify the chemical markers in the cell membrane that tell it when to

stop dividing during development, where to send growing axons, and what other cells to communicate with. Immunological approaches that take advantage of antibodies to these antigenic markers may provide the key to unlock the secrets of neuronal communication. The new techniques of molecular biology may provide means to correct enzymatic defects that distort such neuronal communication and thereby the processing of visual information.

Most of the neurobiological research supported by the National Eye Institute falls into two programs. The Retinal and Choroidal Diseases Program includes support for research related to the many developmental and degenerative disorders of the retina, of which retinitis pigmentosa and macular dystrophy are important examples. Studies are being performed on the structure, function, development, maintenance, and metabolism of the retinal pigment epithelium, the photoreceptors, and the interacting retinal neurons and glia. Special areas of interest include investigations into the conditions which may promote the rescue or regeneration of damaged retinal neurons and the development and application of noninvasive tests of retinal function. In FY 1981 the Retinal and Choroidal Diseases program supported 274 neuroscience-related grants at a total cost of $22.8 million.

The Strabismus, Amblyopia, and Visual Processing Program includes support for research on the growth, development, and modification of the visual system from the optic nerve through all the visual centers of the brain. Specifically, this includes neurotransmitters, molecules that define cell specificity, axonal transport, neuronal specificity, synaptic transmission, neuron differentiation, and neuronal connectivity. Mapping areas of the visual cortex of the brain and the role of efferent and afferent pathways in processing visual information are also areas of current interest. Research to follow up on recent advances in understanding how the brain controls eye movements to fixate or track objects and the influence of these movements on visual perception are also of great importance. Because most of the disorders this program addresses (amblyopia, strabismus, optic nerve atrophies, myopia, and demyelinating diseases) are developmental in nature, there is great interest in devising noninvasive tests of vision in infants and very young children to enable earlier diagnosis and treatment. In FY 1981 the Strabismus, Amblyopia, and Visual Processing program, virtually all of which is neuroscience-related, supported 268 grants at a total cost of $22.3 million. Thus, in FY 1981 the NEI funded a total of 542 neuroscience grants at a total cost of $45 million.

MOLECULAR BIOLOGY

New discoveries in the field of molecular biology have led to an explosive development of techniques that are revolutionizing many aspects of biological science, medicine, and industry. The application of these techniques to vision research may ultimately enable detailed understanding of the molecular aspects of how the visual system develops, the genetic structure and function of the eye, and normal and abnormal visual processes.

In most biological systems, the main repository of genetic information is the deoxyribonucleic acid (DNA) of the chromosomes. Essentially all cells of an organism have the same genetic composition, but, because in a given cell only certain genes are actually expressed, cells differ markedly in structure and function. Most genes in a cell are inoperative most of the time; however, they can be activated by specific signals. When activated, a gene synthesizes a specific ribonucleic acid (RNA) which subsequently directs the synthesis of a unique protein. In its turn, the protein may either become incorporated into the cell's structure, act as a catalyst, or be secreted from the cell to function elsewhere in the organism. If defective, a gene may produce a protein with altered or damaged biological properties, thereby leading to profound changes in the functioning of the entire system.

Through molecular biological research, it is becoming possible for the first time to relate visual processes directly to gene processes. Because several eye disorders—for example, certain types of cataract and retinal degeneration—are now known to be hereditary, it is important to be able to identify and localize the underlying genetic defects. New techniques for producing cell hybrids are helping scientists determine which chromosome carries a particular gene. One application of this technique is the production of interspecies hybrid cells, for example, hybrids between human cells and those of mice. These hybrid cells, containing some human chromosomes and some mouse chromosomes, can then be cloned and grown in culture. Individual clones differ according to which human and mouse chromosomes they contain and correspondingly differ in the patterns of proteins which they produce. Furthermore, these hybrid cells are unstable and tend to lose chromosomes as they grow and divide. Thus, by comparing at intervals the chromosomal content and the protein products of the various cloned hybrids, it is possible to deduce which chromosome carries the gene that codes for a particular protein.

Another application of cell hybridization is the production of hybridomas, which are hybrids between a leukemia cell and an antibody-producing spleen cell. When grown in culture, these hybrido-

mas can be made to produce large quantities of monoclonal antibodies, which can bind to specific structural features of cells. Because the various visual system cell types differ structurally and specific cell types undergo major structural changes during development, monoclonal antibodies permit one to examine, for example, the changes in cellular structure that occur during optic nerve development and to distinguish among the various cell types in the visual system. The ability of monoclonal antibodies to seek out and bind to specific kinds of cells may some day be used to guide drugs to specific target cells for treating certain eye disorders as glaucoma or ocular tumors.

Other perhaps even more far-reaching recent breakthroughs in molecular biology are being accomplished through new methods of combining genes from two distinct cell types into a single piece of functioning DNA. This recombinant approach was made possible through the discovery of a family of enzymes that cuts DNA at a limited number of very specific locations. A piece of DNA containing a certain mammalian gene can then be spliced into a piece of DNA from a second kind of cell. For example, mammalian genes can be inserted into the DNA of bacteria or yeast cells which can be easily grown in large quantities at low cost. This procedure produces many multiple copies of the gene, enabling scientists to isolate and study the structure, arrangement, and expression of mammalian genes. Furthermore, when given the proper signal, the host cells that carry the mammalian genes synthesize large quantities of the protein encoded by that gene. These may be used in additional research or for therapeutic or industrial purposes.

Recombinant DNA techniques are being used to study the gene families that produce structurally and functionally important proteins of the eye, such as the crystallins (lens proteins responsible for transparency), opsins (retinal proteins responsible for the visual signal), and collagens (extracellular proteins that control the shape and structure of the eye). Genes for crystallins and collagens already have been cloned, and the genes for the retinal protein rhodopsin are now being isolated, spliced into bacterial DNA, and produced in large quantity by culturing the bacteria that carry the genes. After isolation from the bacteria, the gene copies will be used in a variety of experiments to examine the activity and structure of genes in normal and diseased eyes and to discover the genetic basis for hereditary disorders in ocular tissues. For example, the large number of gene copies provide enough material to permit the determination of the exact sequence of nucleotides that constitutes a gene. It is important to examine these sequences, because even a single altered nucleotide may lead to faulty function.

Other experiments make use of the fact that DNA normally replicates itself or produces RNA through the synthesis of a complementary copy and that it binds tightly to complementary copies. This propensity of a strand of DNA to bind complementary copies can be used to determine the gene organization in a cell or the number of RNA copies a cell contains, which is a measure of gene activity. These techniques have already made it possible to demonstrate that crystallin gene expression is severely depressed in hereditary and diabetic cataracts. A type of hereditary mouse cataract has been directly associated with a defect in the expression of one specific member of the beta-crystallin gene family. Additional research should explain how and why this gene expression is depressed and may ultimately provide a means of altering the condition. In fact, recombinant DNA techniques will probably make it possible eventually to replace defective genes in humans, thereby providing more effective treatment of a variety of hereditary diseases, including those of the visual system.

In addition to providing information on gene structure and function in the visual system, recombinant DNA techniques are helping to solve some technical problems of research that would be very difficult, if not impossible, with traditional methods. For example, many essential proteins of the visual system occur in vanishingly small quantities. Isolation of sufficient quantities of these proteins to permit studies of their properties would require huge amounts of tissue, perhaps from thousands of animals, and would necessitate very tedious and expensive procedures for purification. Many important studies will now become possible by isolating the genes that code for the proteins, cloning them in bacteria, and using these bacteria to produce large quantities of relatively pure protein that can then be easily purified and characterized. Characterization of proteins in the visual system will be greatly aided by the fact that considerable information about the properties of proteins can now be obtained by determining the nucleic acid sequence of the corresponding genes.

These are but a few of the research opportunities that molecular biology presents for vision research. Discoveries made during the last five or ten years have made possible experimentation that until quite recently was only dreamed of, and many exciting and important advances are promised for the future. The application to vision research of existing techniques and of new ones yet to be developed will not only help us understand more about the visual system and its disorders, but will also open new doors to the correction of these conditions.

NONINVASIVE RESEARCH AND DIAGNOSTIC TECHNIQUES

In the battle against blinding and disabling eye diseases, most progress begins in the laboratory, where animal models are frequently used to test hypotheses concerning etiology and potential effectiveness of newly developed treatments. Eventually the techniques developed in the laboratory must be applied in the clinic, but often the elegant electrophysiological recordings and biochemical manipulations that have proved successful in animal models cannot be applied directly to diagnosing disorders in humans because of their invasive nature, that is, the need to penetrate the eye or the brain. For this reason, the National Eye Institute has had a continuing interest in supporting research designed to assess visual function noninvasively and to use these measurements to identify the dysfunction in particular elements of the visual system. In addition to differential diagnosis of disorders, noninvasive techniques can be used to monitor the progress of therapy.

Each of the five NEI programs supports an increasing range of research on the development and clinical application of noninvasive techniques. The major aims of these techniques are to record externally the electrical activity generated by internal visual structures, to measure behaviorally the sensory experience of patients, to visualize internal structures by external photography coupled with microscopy, or to assess the functional viability as well as structural integrity of various cellular elements.

The Retinal and Choroidal Diseases program supports research on the use of laser and infrared stimuli under computer control to localize very precisely specific areas of the retina. This technique enables exploration of the functioning of tissue surrounding retinal damage. Psychophysical measurements such as the Stiles-Crawford effect, contrast sensitivity functions, and threshold changes with adaptation are revealing mechanisms underlying a variety of retinal degenerations and hereditary disorders. New techniques are also being developed to measure blood flow, vascular permeability, and oxygen saturation without direct contact with the ocular blood vessels. Electroretinography is now permitting detailed indirect measurements of retinal function.

Clinical psychophysical measurements have been used in the assessment of disorders which are the concern of NEI's Strabismus, Amblyopia, and Visual Processing program. Recently developed tests such as preferential looking, derived from animal psychophysics, have permitted assessment of the visual capacities of infants and very young children. The functioning of visual areas of the brain can be measured by the visually evoked potential which may provide a more rapid means of assessing infant vision as well as diagnosing sensory neuro-ophthalmic disorders such as optic neuritis and multiple sclerosis. Eye movement responses to both visual and vestibular stimuli, recorded by electrodes attached to the skin or by corneal reflection techniques, are now considered important in diagnosing a variety of neurological diseases and will continue to be evaluated for this purpose. Optical devices like the laser optometer may prove useful in studying disorders of visual accommodation.

Measurement of corneal endothelial cell density has been made possible by the development of the specular microscope, which can also be used to evaluate the structure of lens epithelial cells. New techniques in spectrofluorophotometry allow assessment of corneal cell function as well as structure. The corneascope is becoming more important as an aid to measuring corneal contour as a preliminary to contact lens fitting, corneal surgery, and assessment of astigmatism. The ultrasound pachymeter has been devised to measure corneal thickness.

Efforts to study the development of cataract noninvasively are being expanded through use of Raman spectroscopy, laser and ultraviolet fluorescence spectroscopy, and ^{13}C and ^{13}P nuclear magnetic resonance. These methods appear to have great promise for revealing in the near future the biochemical alterations in the lens without having to dissect or homogenize it.

The Glaucoma program supports research on noninvasive techniques to measure aqueous humor hydrodynamics; changes in physical properties of the eye in glaucoma; and changes in the structure, vascularity, and appearance of the optic nervehead. These investigations include evaluation of the usefulness of stereophotogrammetry, automated perimetry, and optic disc contouring with a laser in predicting progression of the disease, and development of new approaches to tonometry and tonography.

To realize the enormous potential of noninvasive techniques for diagnosis and for etiological investigations it will be necessary to enlist the combined efforts of clinicians and investigators from a broad range of basic and applied science disciplines, including optics, psychophysics, physiology, and biomedical engineering. In this effort, close cooperation with private industry is not only desirable but frequently crucial. In FY 1981 the NEI funded 81 grants related to noninvasive techniques of visual assessment.

REFRACTIVE ERRORS

Refractive errors of the eye, most commonly nearsightedness (myopia) and farsightedness (hyperopia), affect over 100 million Americans. Although not generally regarded as serious health problems because they almost always can be easily and effectively corrected by eyeglasses or contact lenses, the cost of treating these pervasive conditions amounts to nearly $2 billion a year.

Research relating to refraction is included primarily within two of NEI's programs. In the Corneal Diseases program the subprogram on Refractive Problems and Contact Lenses includes research on contact lenses and on radial keratotomy and other forms of corneal surgery which have recently been introduced as alternatives or adjuncts to eyeglass or contact lens correction of refractive errors. In the Strabismus, Amblyopia, and Visual Processing program the subprogram on Optics and Refractive Errors, Including Myopia, is primarily concerned with the development of refractive errors. Projects supported in this subprogram seek clues to methods of preventing, reversing, or ameliorating refractive errors. Of particular interest are new animal models for refractive errors, which are providing interesting leads to their etiology.

In addition, the Cataract program, through its subprogram on the Treatment of Cataract and Correction of Aphakia, supports research relating to improving optical compensation after removal of the natural lens in cataract extraction. This includes special types of eyeglasses, contact lenses, intraocular lenses, and new methods of corneal refractive surgery. Also, in the Retinal and Choroidal Diseases program the subprogram on Retinal Detachment and Vitreous Disorders supports research relevant to refractive errors because extremely high degrees of myopia place an individual at high risk for retinal detachment. In addition, an extreme variety of myopia called degenerative or pathologic myopia is associated with degeneration of the retina, choroid, sclera, and vitreous body. In FY 1981, the NEI supported a total of 22 projects at a total cost of $2 million for research directly related to refractive errors.

USE OF ANIMALS IN VISION RESEARCH

The National Advisory Eye Council strongly endorses the continued conservative and humane use of animals in vision research. The vast majority of the major advances made in this field over the past several decades have come from animal studies—advances which have saved or restored the vision of millions of people. The recent development of new animal models for human disease offers hope for those now suffering from currently incurable eye problems or for the thousands who will soon encounter unpreventable and untreatable diseases.

At the same time, the Council applauds the efforts of those who seek alternatives to animals for certain types of research. In February 1981, the National Institutes of Health sponsored a symposium on bioassay methodologies in collaboration with other agencies participating in the National Toxicology Program. One aspect of the meeting concerned those assay tasks which now require the use of live animals; particular attention was given to the feasibility of using in vitro or mathematical methods to reduce this dependency. There is a strong interest in the search for alternatives to animal testing; several bills have been introduced into the Congress to promote this effort. Such techniques may allow either elimination of animals from some research or perhaps early testing by an in vitro method, thus reducing the number of animals required for testing. Such alternatives might include the use of bacteria, lower organisms, or cell cultures, as well as mathematical methods.

Certainly, the increasing ability to study diseased or aging ocular cells and tissues in laboratory culture is a significant step toward reducing the need for animals in research. However, until further progress in this area is made, animal research will of necessity continue to be of vital importance in the struggle against human blindness. At present, in vitro testing is not always adequate; some drug testing, for example, must be done in animals to evaluate the biochemical and immunologic reactions in an intact, functioning organism. This is also true for studies on the effects of whole body radiation. And it is possible that cells in culture may behave and react in ways very different from the intact body with operative host defense mechanisms.

Another issue that has emerged concerning the use of animals in vision research is that of the choice of animal species. Present knowledge of visual function is derived from the investigation of a wide variety of species. A significant amount of information relevant to the human visual system has been obtained from the study of nonmammalian and even invertebrate species. Thus, the Council strongly advocates, as it has in the past, that investigators give priority consideration to choosing whatever species is best suited to answering the particular research question posed, and that preference be given to the species offering information that will be the most generalizable to the human condition. Many of the recommendations in this National Plan mention specific species in which research would be particularly valuable.

Finally, the Council has voiced its concern about humane research procedures by issuing in October 1979, a policy statement entitled "Procedures to Assure Freedom from Pain in Experiments Upon Cold-Blooded Vertebrates," a class of research animals often overlooked even by animal welfare advocates.

NOTES

1. Salans LB, Graham BJ (eds): Proceedings of a Task Force on Animals Appropriate for Studying Diabetes Mellitus and Its Complications. *Diabetes* 31(suppl): 1–102, 1982.
2. The Special Foreign Currency Program of the National Institutes of Health utilizes U.S.-owned foreign currencies derived from the sale in foreign markets of surplus agricultural commodities authorized by the Agricultural Trade Development and Assistance Act of 1954, Public Law 480, Subsection 104(b)(3), which permits use of foreign currencies ". . . to conduct and support scientific activities overseas including programs and projects of scientific cooperation between the United States and other countries. . . ."
3. Immunology of the eye; Workshop I: Immunogenetics and Transplantation Immunity. Steinberg GM, Gery I, Nussenblatt RB (eds): *Sp Suppl Immunology Abstracts*, 1980.
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APPENDIX: PLANNING STRATEGY AND PROCESS

BACKGROUND AND HISTORY

THE NATIONAL EYE INSTITUTE has made program evaluation and planning the foundation of both its day-to-day management and its strategy for long-term development. The National Advisory Eye Council's periodically updated five-year National Plan supports NEI staff decision-making and serves as a detailed guide in formulating and implementing policy and determining priorities for the future support of vision research.

In 1975 the NEI Director requested the Council to explore the possiblity of systematically determining program priorities. Their response was a report entitled *Vision Research Program Planning* which contained the first formal description, classification, and assessment of the NEI program; established a rationale and set of guidelines for future planning; and outlined initial program priorities. At that time, as now, there were five factors which in the view of the NEI staff and the Council made program planning imperative:

- The limited resources available for vision research;
- The periodic fluctuations in Federal biomedical research support and their effect upon the continuity of vision research;
- The need for a systematic means of determining the appropriate level of Federal support for vision research;
- The desire of the NEI to be fully accountable to the Administration, the Congress, and the American people for the expenditure of tax dollars for research; and
- The expectation that research planning can enhance the rate of advancement in the sciences related to vision.

Encouraged by the generally favorable response to its first report from the scientific community and from the Congress and Administration officials, the Council in April 1977 published an updated and considerably more detailed report, *Vision Research—A National Plan: 1978–1982.* This three-volume document defined for the first time specific NEI program goals and objectives, systematically assessed recent research and program accomplishments, documented major research needs and opportunities in detail in each NEI program, recommended several program priorities, and identified and justified the resources needed to carry out these recommendations. The present 1983–1987 National Plan, in which an effort has been made to evaluate recent progress and current needs and opportunities in virtually every field of vision research, is the most comprehensive, structured, and detailed to date.

PLANNING PHILOSOPHY

In preparing these Plans, the Council has attempted to make them sufficiently detailed to be meaningful and useful, yet elastic enough to allow the NEI to capitalize on whatever new opportunities may de-

velop unexpectedly from the creativity and ingenuity of the vision research community or from science at large. Because of the very broad representation of vision scientists in the present planning process, the Council and the NEI are confident that this National Plan addresses realistically the most important needs and opportunities that exist in vision research today.

At the very least, this comprehensive approach provides a structure for the examination of the entire NEI program and for the assessment of recent progress. At best, these Plans can facilitate the advancement of scientific knowledge and the conquest of eye and vision disorders. By calling wide attention to research opportunities identified by scientists themselves and stressing their relevance to the solution of important visual health problems and by making a strong case for future program growth and development, program planning has helped the cause of vision research to bring us closer to the eventual elimination of the major eye and visual disorders that plague the Nation.

In carrying out program planning, the NEI and the Council have adopted the following guidelines:

- Research planning procedures must not disrupt the successful ongoing research program of the NEI;
- The Plan should encourage additional research in important areas where activity is low, stimulate initiatives in important areas where work is not now being performed, and reexamine areas where a considerable amount of research is already underway to determine if further expansion is warranted in the near future;
- The individual, investigator-initiated research project grant should continue to be relied upon as the primary mechanism of NEI support;
- Peer review should continue to be depended on for the initial assessment of the scientific merit of proposals for individual research projects;
- All such proposals which are judged by initial review groups to be of the highest scientific quality must be given the highest program and funding priority;
- Nonetheless, research should be emphasized that is most relevant to the prevention, diagnosis, and treatment of the most common blinding and disabling disorders of the eye and visual system;
- When research involves laboratory animals, projects utilizing those species for which both scientific opportunity and technical feasibility permit the greatest amount of generalization to the human condition should be favored;
- Program planning must be a prospective, continuing process in which all data, reports, and recommendations are promptly made available to members of the scientific community and to the general public.

STRUCTURE AND PROCESS

The National Plan is developed under the auspices of the National Advisory Eye Council through a Program Planning Subcommittee assisted by Panels of scientific experts as well as NEI staff and ad hoc consultants from the research community. For the current Plan, six Panels were established, one for each of the five NEI programs plus a special one to consider research needs in the general field of Visual Impairment and Its Rehabilitation. (See Chapter One, Figure 1).

The Chairman and Members of the NAEC Planning Subcommittee are nominated by the NEI Director and agreed to by the full Council. Next, each NEI extramural program director submits to the NEI Director the names of senior investigators who would be likely candidates for Panel chairmen. In the case of the two largest NEI programs—Retinal and Choroidal Diseases and Strabismus, Amblyopia, and Visual Processing—co-chairmen are nominated. The NEI Director, the Chairman of the Program Planning Subcommittee, and the Chief of the NEI Office of Program Planning, Analysis, and Evaluation (OPPAE) consider these nominations along with additional names suggested by other members of the NEI staff and Council and nominate a final slate for review by the Subcommittee as a whole. After a final determination is made, the NEI Director and Subcommittee Chairman co-sign letters of invitation to prospective Panel Chairmen.

After Panel Chairmen have agreed to serve, they are asked to nominate individuals they would like to have serve on the Panel, giving consideration to assembling a group of senior investigators who can adequately represent and consider the full range of basic and applied research in each program. Also, Chairmen are asked to include at least one person who may not have been trained in vision research but who is able to provide a valuable perspective from a related scientific field, for example, genetics, immunology, or biophysics. It is also suggested that an epidemiologist be included on each Panel. At a meeting of the Panel Chairmen, Subcommittee Chairman, NEI Director, and members of the NEI staff, a final list of those who will be invited to serve on the Panels is developed. Panel Chairmen then informally invite the nominees to serve on their

Panels; those who accept are sent a letter of confirmation by the Chief, OPPAE.

Once the Panels are established, arrangements are made for a series of meetings to be held at NIH in Bethesda. These meetings are attended by the Chief, OPPAE, and his staff, by extramural Program Directors who serve as the Executive Secretaries of the Panels for their respective programs, and by the NEI Director and other senior staff members on an ad hoc basis. If possible, the Chairman and/or members of the Planning Subcommittee attend the first meeting of each Panel.

This first Panel meeting lasts two days and is devoted to orientation of Panel members to the NAEC/NEI planning process. A formal charge and tentative timetable is presented to the Panel members and a model outline prepared by the OPPAE and Subcommittee is discussed. An effort is made to assure that each Panel follows essentially the same process in assessing its program, in deciding upon program priorities, and in preparing its report. This assures uniformity in the Plan's format and makes it easier to comprehend the NEI program as a whole and to compare programs. Also at the first meeting, the Panel reviews the current structure of the program to determine if it provides an adequate classification of the current NEI grant portfolio and a reflection of the field of science it represents, keeping in mind that changes in program structure may make it difficult to review historical data on the program. Any changes the Panel would like to make are communicated to the NEI Director through the extramural program staff. Before the Panel meeting is adjourned, the Director decides whether to accept the changes.

Once a final program structure is determined, the Panel Chairman (or Co-Chairmen) assign individual Panel members(s) to write chapter(s) that discuss each subprogram and area according to the model outline. Panel members are encouraged to consult with colleagues and other experts in specialized areas to ensure that no important aspect of research in their assigned field is overlooked. Subsequent to the meeting, the OPPAE mails to each member data on the NEI grants awarded in the fiscal years covered by the last published National Plan in the subprogram he or she has been assigned. These are classified within subprogram according to the priorities identified in that Plan so that it can be determined how closely the actual awarding of grants in those years followed the last Plan's recommendations.

Information is also sent to Panel members about vision research projects supported by other public and private agencies that relate to the goals and interests of the NEI program. (See Chapter One). These are to be considered in making final recommendations to insure against needless duplication between NEI and other agency support.

Panel members mail their first drafts to the OPPAE before the next Panel meeting in sufficient time for them to be entered into the Office's word processing system (to facilitate future revisions and typesetting of the final report), duplicated, and circulated by mail to other Panel members. Subsequent meetings of the Panel—anywhere from two to four depending on the size of the program and the perceived need of the Panel or NEI staff—are held over the next eight to twelve months. At these meetings revised drafts of the report are discussed and revised several times, and eventually a consensus of Panel members is reached on the designation of current and projected research areas as either Program Base or Program Development Priorities (see Chapter One).

Draft Panel reports are then mailed to members of the Program Planning Subcommittee who subsequently discuss them at a meeting that is usually held the day before a regularly scheduled meeting of the full Council. The Subcommittee Chairman reports on these drafts to the Council the following day, and subsequently all Council comments and recommendations are transmitted by the Chief, OPPAE, to the appropriate Panel Chairmen and members.

After considering the Council's comments, the Panels meet again to review final draft reports and to develop Resource Tables which indicate the level of effort the Panels consider reasonable to attain in each area by the first fiscal year covered by the new Plan. These final drafts are reviewed by the Subcommittee and the Council as before, with particular attention given to the Resource Tables which will form the basis for the Council's recommended budget. The Council may ask the Panels to consider either cutting or increasing their projections in specific areas. Depending on the extent of Council comments, the Panels may either meet one final time or respond by means of a conference call. In some cases the final resolution of differences between the Council and the Panels may be delegated to the Panel Chairman or Chairmen.

Over the next several months, the Chief, OPPAE, and his staff work with the NEI extramural program directors and Panel Chairmen and members to complete the Panel reports. The reports are thoroughly edited and put into standard format, and inconsistencies among related sections are resolved. The OPPAE staff also prepares certain sections of Volume One, assembles Volume Three, and works with a graphic artist to develop a design and layout for the entire Plan. When all editorial work is completed, the text of the report is transmitted to the NIH central computer facility and put on-line for OPPAE to do final editing and coding for computerized typesetting by the Government Printing Office (GPO). Camera ready copy is prepared for printing by the NIH Medical Arts and Photog-

raphy Branch and reviewed for the last time by OPPAE staff before being submitted for printing under the auspices of GPO.

The printed report is delivered to the OPPAE which handles its initial and subsequent distribution. The Executive Summary and Volume One are sent to all current NEI grantees, members of the Association for Research in Vision and Ophthalmology, members of the Association of University Professors of Ophthalmology, Deans of Schools and Colleges of Optometry, representatives of government agencies and private organizations that support vision research, and key NIH officials. Copies of the individual parts of Volume Two are mailed to NEI grantees in each of the five NEI programs as appropriate. A return postal card included with Volume One provides recipients the opportunity to request whatever other portions of the Plan they wish to receive as well as extra copies of those they have or will receive automatically. Complete sets of the entire Plan are sent to all members of the Council and Panels.

TRACKING

Soon after the final delineation of the Research Base and Program Development Priorities in each program, the OPPAE establishes a computerized system for tracking all grant applications beginning in the fiscal year preceding the period covered by the new Plan. This system includes coding each application according to its relevance to an element of either the Program Base or Program Development Priorities in the subprogram to which it has been assigned. The few applications which cannot be placed in one of these categories are assigned a miscellaneous code. Following each Council meeting, those applications which are approved and funded are so designated in the system. A report is generated prior to the next Council meeting which shows the correspondence between projected and actual funding in each Program Base or Program Development Priority area. This information is used by the Council in making Program Relevance decisions and serves as an evaluation data base which is used in the development of the National Plan for the next five-year period.

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